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Developing and piloting an intervention for the management of inflammatory bowel disease-fatigue

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**Developing and piloting an
intervention for the management of
inflammatory bowel disease-fatigue**

Micol Artom

*A thesis submitted in partial fulfilment of the
University's requirements for the Degree of Doctor of
Philosophy*

12th March 2018

King's College London
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Abstract

Background: Fatigue is a complex, multifactorial and multidimensional phenomenon, which has been described as a persistent overwhelming sense of tiredness, weakness, or exhaustion. It is the third most common concern for patients with inflammatory bowel disease (IBD), experienced by 44-86% of patients with active disease and 22-41% of patients in remission. Fatigue can have a significant negative impact on patients' quality of life (QoL). The aetiology of fatigue is not well understood. Interventions for IBD-fatigue are scarce, demonstrating limited benefit, and have not been implemented into clinical practice. The development of a theoretically-driven intervention to improve fatigue is a primary need for this population.

Methods: The overall aim of the study was to develop a complex intervention for the management of IBD-fatigue and test its feasibility and potential efficacy. Guided by self-regulation theory and the Medical Research Council framework for development, feasibility and piloting phases, four steps were conducted in an iterative process. A systematic review study (Paper 1), identified aetiological modifiable factors which had already been or could be targeted by health interventions to improve IBD-fatigue. A quantitative cross-sectional study ($n = 182$) (Paper 2), evaluated the potential relationship between the identified modifiable cognitive-behavioural factors and IBD-fatigue. Patient and public involvement activities informed the adaptation of a cognitive-behavioural therapy (CBT) intervention for multiple-sclerosis fatigue to IBD-fatigue. Lastly, a two-arm pilot randomised controlled trial (RCT) with a nested qualitative study (Papers 3 and 4) assessed the feasibility and initial estimates of efficacy of a CBT manual with 8, weekly therapist telephone session ($n = 15$) vs. a fatigue information sheet without help ($n = 16$).

Results: Initial estimates of efficacy with per protocol analysis showed a reduction in fatigue scores and an improvement in QoL scores at 3-months post-randomisation. The difference in change in scores between groups was significant for impact of fatigue. The intervention was acceptable to participants and feasible for therapists to deliver. Healthcare professionals working with IBD patients reported that the intervention would be broadly applicable but time, finance and training constraints may limit its implementation in routine clinical care.

Conclusions: CBT for IBD-fatigue is feasible and has a potential for improvement of the impact of fatigue on daily activities. A large-scale RCT is needed to investigate the size and longevity of treatment gains and the cost-effectiveness of the therapy. Incorporating changes to the protocol and developing an online intervention may be an effective way to overcome the barriers to implementation identified by healthcare professionals and test the generalisability of the intervention to IBD-clinical practice.

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Author declarations

During the period of registered study in which this thesis was prepared the author has not been registered for any other academic award or qualification. The material included in this thesis has not been submitted wholly or in part for any academic award or qualification other than that for which it is now submitted. All material in this thesis is original and is the author's own work.

Acknowledgements

Thank you to my supervisors, Professor Christine Norton, Professor Jackie Sturt and Dr Wladzia Czuber-Dochan. Their knowledge, guidance and support are what enabled me to start, and more importantly, to persevere to the end of this PhD. I am looking forwards to pursuing new goals together with you in the coming years.

Thank you to Professor Rona Moss-Morris for lending me her expertise and her work on fatigue in multiple sclerosis. Thank you also to Dr Lesley Dibley, her wisdom in times of need has been invaluable. I also owe thanks to Miss Tiffany Wade for her skilful help with the intervention manual, to Mrs Cally Abigail for data inputting with precision and to Mrs Dawn Evans for transcribing the study interviews with speed and proficiency.

Thank you to Mrs Julie Duncan, Dr Peter Irving, Professor Jeremy Sanderson and the whole of the IBD team at GSTT, this project would not have been achieved without your cooperation. Thank you also for providing me with so many opportunities for learning about IBD. Your passion about this condition has inspired me to continue working in this field.

To Miss Louise Sweeney, thank you for joining me in the endeavour to make psychology part of IBD management. Thank you to Mrs Claudia Leone and the rest of the PhD student cohort, going through this process together allowed me to find strength even in moments of struggle. Thank you to my family and friends for never questioning I would reach the finish line.

List of papers

1. Artom, M., Czuber-Dochan, W., Sturt, J. and Norton, C., 2016. Targets for Health Interventions for Inflammatory Bowel Disease-fatigue. *Journal of Crohn's & Colitis*, 10(7), 860-869.
2. Artom, M., Czuber-Dochan, W., Sturt, J., Murrells, T. and Norton, C., 2016. The contribution of clinical and psychosocial factors to fatigue in 182 patients with inflammatory bowel disease: a cross-sectional study. *Alimentary, Pharmacology & Therapeutics*, 45(3), 403-416.
3. Artom, M., Czuber-Dochan, W., Sturt, J. and Norton, C., 2017. Cognitive behavioural therapy for the management of inflammatory bowel disease-fatigue with a nested qualitative element: study protocol for a randomised controlled trial. *Trials*, 18(1), 213-226.
4. Artom, M., Czuber-Dochan, W., Sturt, J. and Norton, C., 2018. Cognitive behavioural therapy for the management of inflammatory bowel disease-Fatigue: a pilot randomised controlled trial. *Submitted for publication*

List of abbreviations

AZA	Azathioprine
BIPQ	Brief Illness Perceptions Questionnaire
CBSQ	Cognitive Behaviour Responses to Symptoms Questionnaire
CBT	Cognitive behavioural therapy
CCUK	Crohn's and Colitis United Kingdom
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CINHAL	Cumulative Index to Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
CPSS	Cohen Perceived Stress Scale
DAI	Disease activity index
ESS	Epworth Sleepiness Scale
GAD7	Generalised Anxiety Disorder Assessment
GI	Gastro-intestinal
GP	General Practitioner
KCL	King's College London
HADS	Hospital Anxiety and Depression Scale
HBI	Harvey Bradshaw Index
HCP	Healthcare professional
HR	Hazard ratio
IBD	Inflammatory Bowel Disease
IBDU	Inflammatory Bowel Disease Unclassified
IBD-D	Inflammatory Bowel Disease-Distress Scale
IBD-F	Inflammatory Bowel Disease-Fatigue
IBDQ	Inflammatory Bowel Disease Questionnaire
IBS	Irritable bowel syndrome
IM	Intervention modelling
MFI	Multidimensional Fatigue Inventory
MRC	Medical Research Council Framework
MS	Multiple sclerosis
MTX	Methotrexate
NHS	National Health Service
OR	Odds ratio
PHQ-9	Patient Health Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
SCCAI	Simple Clinical Colitis Activity Index

SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TIDieR	Template for Intervention Description and Replication
TNF	Tumour necrosis factor
UC	Ulcerative Colitis
UK	United Kingdom
5-ASAs	5-aminosalicytic acid compounds
6-MP	6-mercaptopurine

Chapter 1

1. Introduction

1.1. Background to inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) mainly encompasses two related but distinct conditions of the gastrointestinal tract, ulcerative colitis (UC) and Crohn's disease (CD) (Silverberg et al., 2005). UC is characterised by diffuse mucosal inflammation limited to the rectum and colon. Disease extent can be broadly divided into distal and more extensive disease. Distal disease refers to colitis limited to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis). More extensive disease includes left-sided colitis (up to the splenic flexure), extensive colitis (up to the hepatic flexure), and pancolitis (affecting the whole colon) (Dignass et al., 2012). CD is characterised by patchy, transmural inflammation, affecting any part of the gastrointestinal tract from the mouth to the anus. It may be defined by pattern of disease (inflammatory, fistulating, or stricturing) or by location (terminal ileal, colonic, ileocolic, upper gastrointestinal) (Van Assche et al., 2010, Baumgart and Sandborn, 2016). Lastly, inflammatory bowel disease unclassified (IBDU) is a diagnosis/classification for patients for whom the endoscopy is inconclusive and histology reveals chronic inflammation with absence of definite diagnostic features of either CD or UC (Silverberg et al., 2005). For most patients, IBDU represents a temporary diagnosis, as it has been estimated that 80% of them will be reclassified to either CD or UC within eight years (Meucci et al., 1999).

1.1.1 Clinical features of IBD

The cardinal symptom of UC is bloody diarrhoea, associated at times with abdominal pain, urgency, tenesmus and fatigue (Stange et al., 2008, Dignass et al., 2012). Its clinical course is marked by exacerbation and remission. About 10% of patients need a colectomy at some point in the disease trajectory (Solberg et al., 2009). Symptoms of CD are more heterogeneous, and usually include abdominal pain, diarrhoea and weight loss. Extra-intestinal symptoms such as fever, malaise, anorexia and fatigue are also more common. Furthermore, CD may lead to intestinal obstruction due to fistulae, strictures or abscesses, which may need to be addressed surgically to minimise the disease (Baumgart and Sandborn, 2016). Although the risk of surgery 1, 5, and 10 years after diagnosis has decreased significantly over the past half a century (Frolkis et al., 2013), 70-80% of patients with CD may still require surgery within their lifetime, depending on disease severity and location (Burisch et al., 2013).

1.1.2 Diagnostic investigations

A single diagnostic instrument for the diagnosis of IBD is not available. The diagnosis is confirmed by clinical evaluation and a combination of radiological, endoscopic, histological,

and/or biochemical investigations, and the absence of alternative diagnoses (Hanauer and Sandborn, 2001, Kornbluth and Sachar, 2010). Imaging studies have a limited use in establishing diagnosis; computerised tomography and magnetic resonance imaging might show alterations in the small bowel but are not specific or sensitive enough to be diagnostic tools (Panes et al., 2013). Markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein can be elevated or normal in patients with IBD (Menees et al., 2015). Faecal calprotectin, a protein detectable in stool that correlates with increased neutrophils in the intestine, can be utilised in ruling out a diagnosis, since patients with low faecal calprotectin have a less than 1% chance of having IBD (Sands, 2015). This biomarker has also been shown to predict persistent inflammation (Cerrillo et al., 2015, Yamaguchi et al., 2016) and risk of relapse (Molander et al., 2015, Ferreiro-Iglesias et al., 2016). A full endoscopy with biopsies examined for histological features of IBD is the only way to establish the diagnosis of IBD with certainty (Annese et al., 2013).

1.1.3 Disease activity vs. disease severity assessment

Disease activity and disease severity in IBD refer to two distinct yet overlapping concepts. Disease activity reflects a cross-sectional assessment of inflammatory activity, whereas overall disease severity may include longitudinal and historical factors which give a more complete picture of the global burden of disease (Siegel et al., 2016b). Patients may have severe disease warranting aggressive therapies even if their disease activity is not severe at that point in time. However, placing a value on disease activity and severity is inherently difficult in IBD and is hampered by a lack of validated instruments with discrete thresholds. This is particularly problematic when considering that most treatment algorithms in IBD begin with classifying patients according to disease severity, and most therapies with regulatory approval are for use according to a patient's disease severity at a particular point in time (Peyrin-Biroulet et al., 2013).

No single IBD biomarker can accurately measure disease severity in IBD (Siegel et al., 2016a). Disease activity indices (DAIs) are therefore generally employed to quantify disease activity, clinical remission and response to treatment (Bojic et al., 2016). Numerous DAIs exist, but the most commonly used are the Mayo score (Schroeder et al., 1987) and the Simple Clinical Colitis Activity Index (SCCAI) (Walmsley et al., 1998) for UC and the Crohn's Disease Activity Index (CDAI) (Best et al., 1979) and the Harvey Bradshaw Index (HBAI) (Harvey and Bradshaw, 1980) for CD. However, the relationship between gastro-intestinal (GI) symptom reporting and disease activity defined using objective measures of mucosal inflammation is poor. DAIs reflect symptom reporting behaviour rather than disease activity per se (Targownik et al., 2015, Gracie et al., 2016). Furthermore, DAIs have been criticised for a lack of objectivity (Bojic et al., 2016), a low specificity and sensitivity of symptoms included, and for failing to capture the impact of disease from the patient's perspective (Bodger et al., 2014).

Intestinal damage begins soon after onset of inflammation, sometimes in the absence of significant symptoms captured by DAIs. Moreover, IBD can have a significant impact on patients even when they are not experiencing symptoms, which are usually associated with active disease. There is hence the need to think beyond current clinical symptoms to include other factors important to the patient (Peyrin-Biroulet et al., 2016a). The development of validated and reproducible measures of IBD severity, accounting for current disease activity, assessment of cumulative bowel damage and quality of life (QoL) is essential (Peyrin-Biroulet et al., 2016b). Measuring disease severity using composite criteria that incorporate (a) impact of disease on patient (clinical symptoms, QoL, fatigue and disability); (b) inflammatory burden (disease activity and extent); and (c) disease course (structural damage, surgery, number of flares, and extraintestinal manifestations) (Levesque et al., 2015, Siegel et al., 2016b) may therefore be the most promising way forward.

1.1.4 Epidemiology of IBD

IBD is a lifelong condition, presenting in adolescence in 25% of the IBD population (mean age range at diagnosis is between 33.4 and 45 years; median age at diagnosis is 29.5 years) and follows an unpredictable relapsing and remitting course (Loftus et al., 2002). CD and UC have classically been thought to demonstrate a bimodal age distribution (*i.e.* with an incidence peak in the second and third decades of life followed by a second, smaller peak in the later decades), however recent epidemiologic studies (Jeuring et al., 2016, Sturm et al., 2016) have not uniformly found the same results. It may be suggested that these differences in age distribution are a representation of variations in diagnostic criteria and/or classification (Loftus, 2004).

IBD occurs across the world but with considerable variations in both incidence and prevalence, both within and between geographic regions (Burisch and Munkholm, 2015). The highest incidence rates are found in Northern Europe (Burisch et al., 2013, 2014) and North America (Bernstein et al., 2006a, Loftus et al., 2007), with the illness being more common in industrialised than non-industrialised countries. IBD affects an estimated 2.2 million people in Europe (Cosnes et al., 2011). The overall prevalence of IBD in the United Kingdom (UK) is about 300 000, with incidence ranging between 8.8 to 14.3 UC and 5.6 to 8.6 CD patients per 100 000 population per year (Bardhan et al., 2010). Overall the incidence of IBD has considerably increased between the 1950s and the 1980s (Logan, 1998, Loftus et al., 2007) and has subsequently continued to increase at a slower rate (Gunesh et al., 2008, Molodecky et al., 2012). To date the increase in incidence of both CD and UC in North America and Europe is fairly stable, however the prevalence of IBD is expected to increase further due to early age of onset and low mortality rates (Molodecky et al.,

2012, Ng et al., 2017, Burisch et al., 2013). Conversely, since 1990, incidence has been rising in newly industrialised countries in Africa, Asia and South America (Ng et al., 2017).

Several important diagnostic changes have been introduced in recent years, which may contribute to an apparent increase in IBD incidence. These include: advances in imaging techniques, changes in mode of diagnosis, optimisation of general practitioner (GP) referral routines and growth in awareness of disease (van den Heuvel et al., 2017). However, a recent retrospective study in Italy (Cantoro et al., 2017) has shown that although there has been a decrease in the proportion of patients with a diagnostic delay over 24 months, there has been no change in the median diagnostic delay of IBD in the last six decades. The median diagnostic delay was significantly longer in CD than UC, with more than one-third of patients with CD being misdiagnosed as irritable bowel syndrome (IBS). As a delay in the diagnosis of IBD has been found to be a risk factor for the development of complications and surgery (Schoepfer et al., 2013, Li et al., 2015), efforts should be spent to develop effective pathways for early detection of IBD.

1.1.5 Risk factors for IBD

The precise aetiology of CD and UC is not presently known (Lees et al., 2011). The chronic intestinal inflammation that characterises IBD results from a complex interplay between the immune system, the host genotype, and the intestinal microbiota. However, the currently identified susceptibility genes only account for a fraction of disease risk, with genetics explaining only 7.5% of disease variance (Jostins et al., 2012). This and the rising incidence of IBD worldwide underline the effect of environmental factors such as smoking which influence disease onset and progression. It is suggested that everyone is born with a certain genetic susceptibility for IBD and exposure to environmental factors in the Western lifestyle and living environment can reach a certain threshold, after which IBD is developed (van der Sloot et al., 2017). Identifying modifiable environmental factors is challenging, and whereas the summation of environmental factors may be crucial, each individual factor may confer only a modest risk (Maaser et al., 2017). Indeed, no single factor alone is sufficient for development of disease (Parkes et al., 2014, Ananthakrishnan, 2015, 2018). Furthermore, risk factors for IBD vary across countries. For instance, certain risk factors that are significant in developed countries may not have the same effect in developing Asian or Middle Eastern populations (Ng et al., 2014).

Women and men are diagnosed in more or less equal numbers (Rubin et al., 2000, Ponder and Long, 2013). However, incidence is influenced by race and ethnicity. The risk of IBD is three-fold higher in the Jewish population than in the non-Jewish population (Bernstein et al. 2006b), with Ashkenazi Jews being at particularly high risk. However, this could be an inflated incidence resulted from methodological issues in the prevalence study designs (Ekbom, 2004). Twin and

genetic studies have suggested a key heritable component for both CD and UC (Ananthakrishnan, 2015). Between 2% and 14% of patients with CD, report a family history of the condition whereas a small proportion of CD patients will have a family history of UC. A similar proportion, 8–14%, of patients with UC will have a family history of IBD, more commonly UC. Consequently, the relative risk of developing IBD for first-degree relatives of a patient with CD is estimated to be around 5% in non-Jewish and 8% in Jewish patients, with the corresponding risk of UC being 1.6% and 5.2%, respectively (Yang et al., 1993). If both parents were affected, the risk of the offspring developing IBD before the age of 30 years is estimated to be as high as one-in-three (Halme et al., 2006). In the future, results of studies such as the Genetic Environmental Microbial Project, following healthy individuals who are at a higher risk of developing disease over time, will aid in determining possible causes for CD.

Meta-analytic data have quantified the increase in risk associated with smoking to be twofold for CD (Maaser et al., 2017, Mahid et al., 2006, To et al., 2016a). Since the 1980s, it has been established that cigarette smokers may be less likely to develop UC than non-smokers (Harries et al., 1982). However, the suggestion that smoking may improve the natural history of UC has recently been questioned. Smoking, when compared to non-smoking, does not appear to have any positive effect on colectomy rates, reduction in the rates of flare of disease activity, proximal disease extension, or the development of pouchitis in patients with UC included in a systematic review (To et al., 2016b). Given the high morbidity and mortality associated with smoking, it may therefore be a risk to advise patients on the benefits of smoking on disease outcomes in UC. For a large number of environmental factors possibly in IBD, meta-analyses are not available yet and the level of evidence provided by individual studies remains low. Therefore more studies are needed before firm conclusions and recommendations concerning adaptation of lifestyle and living environments to prevent and/or treat IBD can be given (van der Sloot et al., 2017).

1.1.6 Societal and economic impact of IBD

The impact of IBD on society is disproportionately high (Carter et al., 2004), with a hospital serving a population of 300 000 typically seeing 45–90 new cases per annum and having 500 under follow up (Loftus, 2004). There is a small increase in mortality for both UC (hazard ratio [HR] 1.44, 95% confidence intervals [CI] 1.31 to 1.58) and CD (HR 1.73, CI 1.54 to 1.96), largely dependent on age and distribution of disease (Card et al., 2003). CD and UC cause substantial economic burden on the healthcare system, including both direct and indirect expenditures. IBD ranks as the first of the five most expensive GI disorders, despite being the lowest in prevalence (Stone, 2012). Direct medical costs include expenses for hospitalisations, physician services, prescription medicines, diagnostic procedures and specialised nursing care (Kappelman et al., 2008). Indirect costs are the value of lost earnings or productivity; they may include the value of

leisure or time lost. Indeed, employed patients with IBD, even when in complete clinical remission, report experiencing decreased productivity significantly more frequently compared to controls (Zand et al., 2015). Furthermore, the cost of IBD has increased over the past decade due to the changing cost-drivers of disease management. The evolution of treatment for CD and UC with the approval of the more effective but more costly tumour necrosis factor (TNF) inhibitors has changed the landscape of treatment and cost for IBD (Mehta, 2016). Whereas anti-TNFs have decreased acute care costs, including hospitalisations and emergency visits, they have substantially increased pharmacy utilisation costs (Park et al., 2016).

The high manufacturing costs and long duration of development have been identified as the main contributors to the high cost of biological medicines. For this reason there has been a recent switch from originator biological medicines to biosimilars, which are usually priced 15-30% below their reference products in Europe. A biosimilar is a biological medicine that enters the market after the expiration of the patent of an original reference product and shows no clinically meaningful differences in terms of quality, safety and efficacy when compared to the reference product (Gecse et al., 2013). Two infliximab biosimilars are currently approved in Europe for use in both CD and UC. The increasing use of these drugs and the possible addition of further biosimilars in the future may likely change the landscape of biologic agents in IBD and the consequent cost expenditure in IBD (Danese et al., 2015).

1.1.7 Overview of drugs for the management of IBD

Over the last decade, several new drugs have been introduced for the treatment of UC and CD. Therapy for IBD is a rapidly evolving field, with many new biological agents under investigation that are likely to change therapeutic strategies radically in the next few years (Mowat et al., 2011). UC is conventionally managed with a step-up algorithm that considers disease activity and response to treatment. 5-aminosalicylic acid compounds (5-ASAs) comprise the base of the therapeutic pyramid followed in sequence by corticosteroids, immunosuppressives and biologics (Chande et al., 2015a). Similarly, current guidelines for CD recommend a step-up strategy consisting of progressive intensification as disease severity increases. Less toxic drugs are used in mild disease, whereas more efficacious but more toxic drugs are employed in severe disease or in patients who are not responsive to first-line therapy.

However, with the advent of biologics, a reversal of the traditional therapeutic pyramid (bottom-up approach), with an early introduction of more aggressive drugs for CD has been advocated by some (Spurio et al., 2012). Conventional management of CD following a sequence of treatment from corticosteroids, to immunomodulators to biologics might not adequately control the underlying inflammation and could delay the start of the most effective treatment (Khanna et al.,

2015a). The top-down approach aims to do more than just controlling symptoms (Colombel and Mahadevan, 2017). Indeed, symptoms are not necessarily indicative of endoscopic status in CD patients and may not be adequate criteria to guide adjustment of treatment to control mucosal inflammation (Colombel et al., 2017). Nonetheless, although the use of biologics as first line treatment may be ‘disease-modifying’, if patients fail to respond to biologics, it will be less likely for them to achieve remission with a second biologic agent or another drug, leaving fewer therapeutic options (Rogler, 2013). Overall, rather than applying a universal treatment strategy to all patients, severity of disease at presentation and/or biomarkers (Colombel et al., 2017) may ultimately guide therapy in newly diagnosed CD patients (Rutgeerts, 2012). A brief overview of the major drug options for IBD, following a therapeutic treatment pyramid (Figure 1) is presented below.

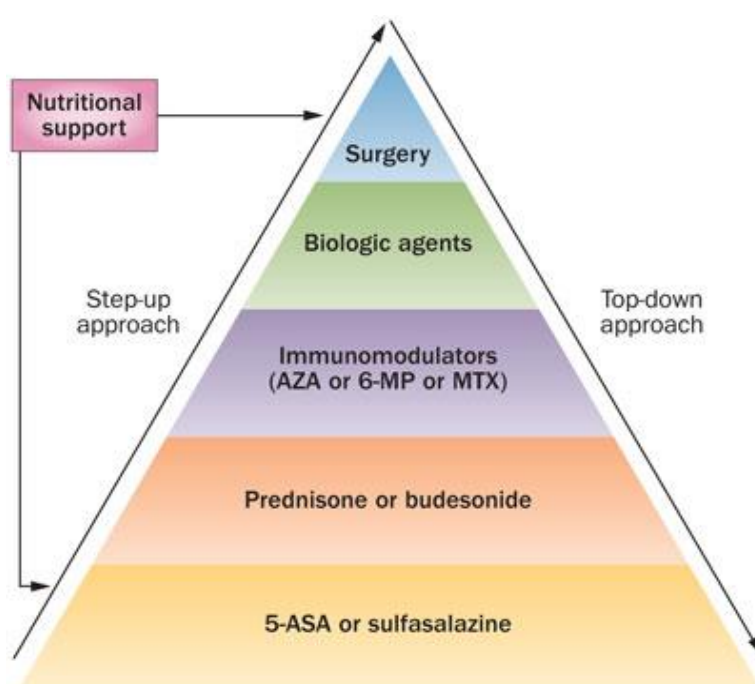


Figure 1: Therapeutic pyramid for IBD management.

Taken from Aloï, M., et al. 2014. Advances in the medical management of paediatric IBD. *Nature Reviews Gastroenterology & Hepatology*, 11(2), 99-108.

Abbreviations: 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; AZA, azathioprine; MTX, methotrexate

1.1.7.1 First line therapy (5-ASAs)

5-ASAs can be delivered by oral tablets or as topical agents in the form of liquid or foam enemas or suppositories. They act on the gut epithelial cells by a variety of mechanisms to moderate the release of lipid mediators, inflammatory cells, cytokines and reactive oxygen species. The main role for 5-ASAs is maintenance of remission of UC (Sandborn and Hanauer, 2003).

1.1.7.2 Second-line therapy (Corticosteroids)

Corticosteroids are potent anti-inflammatory agents for moderate to severe relapses of both UC and CD. They have no role in maintenance therapy for both diseases and act through inhibition of several inflammatory pathways. The efficacy of steroids should be balanced against the potentially severe side effects (Hanauer, 2002). However, the treatment of IBD active disease with steroids is often ultimately appreciated by the patients because it can relieve them rapidly from challenging symptoms (Schiro and Stein, 2015). Three broad groups of side effects can be identified: i) effects due to supra-physiological doses such as cosmetic, sleep and mood disturbance, dyspepsia or glucose intolerance; ii) effects due to prolonged use such as cataracts, osteoporosis, osteonecrosis, myopathy, sepsis and susceptibility to infection; iii) effects due to withdrawal such as adrenal insufficiency, myalgia, malaise and arthralgia. Enteral nutrition is increasingly used for remission induction in children with CD, to minimise the use of steroids (Connors et al., 2017).

1.1.7.3 Third-line therapy (Immunomodulators)

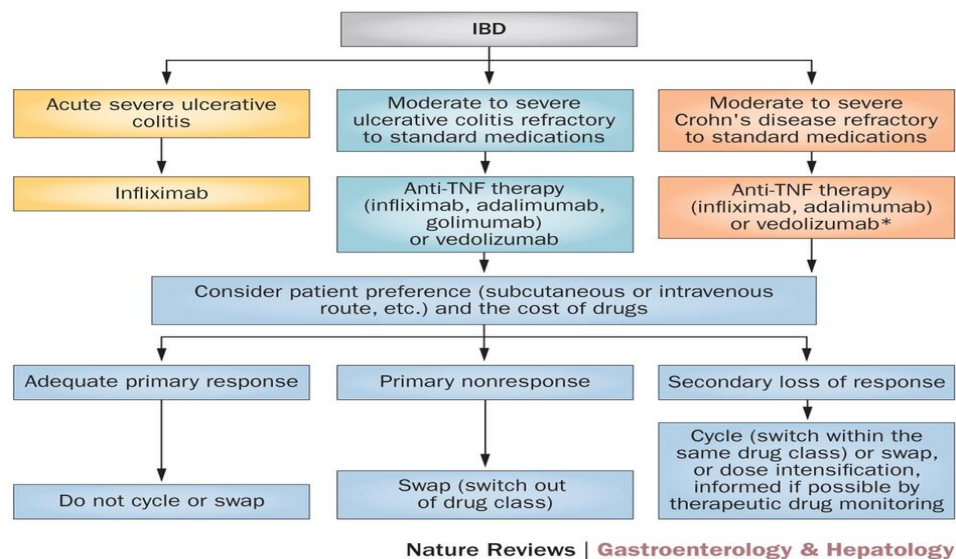
The main immunomodulators utilised in IBD are thiopurines and methotrexate. Thiopurines are designed to suppress the normal activity of the body's immune system. They are widely used in IBD as adjunctive therapy and as corticosteroid-sparing therapies, although their slow onset of action precludes usage as sole therapy for active disease. Thiopurines are effective in steroid dependent UC, they are also effective maintenance therapy for patients who require repeated courses of steroids (Timmer et al., 2016). In CD, thiopurines are effective in both induction and maintenance of remission (Chande et al., 2015b). Nonetheless, adverse events occur in about 20% of patients taking thiopurines. The most common are allergic reactions, which occur soon after induction and cease rapidly subsequent to the drug being withdrawn. Leucopenia, bone marrow toxicity, hepatotoxicity, pancreatitis are rare (Derijks et al., 2006). Frequency of malignancies are reported in other patient populations on thiopurines (Buell et al., 2005), however these findings are not confirmed in patients with IBD (Ariyaratnam and Subramanian, 2014, Jess et al., 2014). Recently, thiopurine metabolite measurement can provide guidance when an adequate response is not reached, including if nonadherence is at issue (Dubinsky, 2004).

Methotrexate is a folic acid antagonist which inhibits purine synthesis, deoxyribonucleic acid and ribonucleic acid formation, and suppresses inflammation in chronic inflammatory conditions through a complicated cascade (Alfadhli et al., 2004, Chande et al., 2014). Methotrexate is mainly utilised in CD and it is contraindicated in pregnancy because of the potential teratogenicity. Currently, it is recommended that females and males stop methotrexate therapy 3 months before planned pregnancy, and that methotrexate should not be used during pregnancy or breast feeding (Feagins and Kane, 2009). Methotrexate has been found to be superior to placebo for the

maintenance of remission at 40 weeks (Patel et al., 2014). While 25mg/week of intramuscular methotrexate provides benefit for induction of remission and complete withdrawal from steroids, lower dose oral methotrexate does not appear to provide any significant benefit relative to placebo or active comparator for CD (McDonald et al., 2012).

1.1.7.4 Fourth-line therapy (Biologics)

Biological therapies are designed to block or neutralise pro-inflammatory cytokines, which play a major role in the pathogenesis of IBD. The initial biologics licensed in the UK (infliximab, adalimumab and golimumab [UC only]) have been monoclonal antibodies against TNF. Infliximab is given as intravenous infusions; adalimumab and golimumab are given as a subcutaneous injection. Two infliximab biosimilars are also approved in Europe (Danese et al., 2015). Meta-analytic results have shown that both anti-TNF agents (infliximab and adalimumab) result in a higher likelihood of induction of remission and response compared to placebo in CD (Stidham et al., 2014a). Likewise, all anti-TNF agents (infliximab, adalimumab and golimumab) result in higher likelihood of induction of remission and response compared to placebo in UC (Stidham et al., 2014b). Currently, the choice of a biologic agent for the treatment of IBD is therefore primarily empiric and based on patient and physician preferences (Figure 2). In absence of comparative, head to head studies it is unclear whether any of these agents is more effective than the other (Miligkos et al., 2016).



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Figure 2: Biologic agents in IBD: a proposed algorithm for practice.

Taken from Danese, S., et al. 2015. Biologic agents for IBD: practical insights. *Nature Reviews of Gastroenterology Hepatology* 12(9), 537-545.

Abbreviations: anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease

Despite established efficacy and safety of anti-TNF agents, they are not effective in one-fifth of individuals in whom they are administered (primary non-response) (Allez et al., 2010, Chowers et al., 2010). An additional one-third will eventually fail therapy (secondary loss of response) (Gisbert and Panés, 2009). Indeed, most of the current evidence does not give an indication of the expected efficacy of anti-TNF agents beyond one year. Findings have shown that 30.6% of 229 UC patients had discontinued infliximab at three years due to adverse events or lack of effect (Reinisch et al., 2012). Similarly, sustained clinical benefit for adalimumab was observed only in 61.5% of 168 CD patients during a median follow-up of 20 months (Karmiris et al., 2009). The overall risk of relapse after discontinuation of anti-TNF therapy has been found to be 44% for CD (912 patients) and 38% for UC (266 patients) (Gisbert et al., 2016). Unfortunately, no definite criteria that can predict response with these agents have been discerned to date, however assays are emerging that can reliably measure both antibodies to anti-TNF and circulating drug levels (Bernstein, 2015). Therapeutic drug monitoring makes it possible to determine if modifications to the drug regimen are required to increase concentrations or whether the patient should be switched to another treatment (Chaparro et al., 2011).

Anti-TNF therapies share a similar profile of adverse events, including increased risk of infections from intracellular pathogens, most notably, tuberculosis, other opportunistic infections, autoimmunity, infusion reactions, and other more rare side effects. This should be balanced with the potential curative option of surgery in UC (Singh et al., 2011a, Mowat et al., 2011). In the future, biological therapies for both CD and UC will be used selectively based on personalised benefit/risk assessment and will be optimised throughout the course of treatment. Choice of therapy will depend on individual patient profiles, determined through reliable biomarkers and tissue signatures. Drug monitoring will be part of treatment optimisation (D'Haens et al., 2014).

Vedolizumab is a gut-selective $\alpha 4\beta 7$ integrin antagonist, which has recently been approved for use in IBD patients. It has a longer effect compared to anti-TNF agents. Results from the GEMINI clinical trials have demonstrated that vedolizumab met primary endpoints for improvement in clinical response at 6 weeks and for clinical remission at 52 weeks (Feagan et al., 2013, Sandborn et al., 2013). Specifically among patients who had previously failed anti-TNF, although efficacy rates were lower than when vedolizumab was used as first-line therapy, a higher proportion of the population given vedolizumab was in remission (26.6%) at 10 weeks than those given placebo (12.1%) (Sands et al., 2014). This suggests that vedolizumab could be considered an added therapeutic option in the treatment pyramid for patients who have failed other therapies. However, currently the lack of comparative efficacy studies, makes the efficacy-to-safety ratio difficult to establish (Regueiro et al., 2016).

Ustekinumab is a monoclonal antibody that neutralizes both IL-12 and -23. Ustekinumab has recently been approved by the National Institute for Health and Clinical Excellence in July 2017 for the treatment of moderately to severely active CD, for adults who have had an inadequate response with, lost response to, or were intolerant to other therapies. Evidence from a Cochrane review (Khanna et al., 2015b) suggests that ustekinumab may be effective for induction of clinical improvement in CD. Since the publication of the Cochrane review, ustekinumab was tested in two induction trials, UNITI-1 and UNITI-2 (Feagan et al., 2016). Patients with moderately to severe CD receiving intravenous ustekinumab had a significantly higher rate of response than did those receiving placebo. Subcutaneous ustekinumab maintained remission in patients who had a clinical response to induction therapy. Nonetheless, it remains unclear whether ustekinumab is an effective agent for induction of remission. Further longitudinal data are required to determine the long-term efficacy and safety of ustekinumab over time.

1.1.8 Impact of IBD on patients' lives

In addition to taxing patients with a number of symptoms, IBD can exert a substantial impact on patients' daily life, affecting work, personal relationships and education (O'Connor et al., 2013). Disease flares can be intense and the related physical symptoms, such as diarrhoea, abdominal pain and fatigue can significantly affect daily functioning. For most IBD patients, life-long pharmacological treatment is required, which is accompanied by side effects, which can be severe (Gearry et al., 2004, Stallmach et al., 2010, Schiro and Stein, 2015). Moreover, many patients require surgery, sometimes leading to a permanent ileostomy or colostomy. Finally, chronic immune suppression increases the risk of haematological malignancies and colitis is associated with an increased risk of colorectal cancer (Lukas, 2010). Thus, IBD affects patients' daily life due to physical impairments, lifelong surveillance, treatment side effects, its unpredictable course, and the risk of malignancy (Annese et al., 2015).

Due to the severity of IBD, emotional burden and psychological distress is also common (Keeton et al., 2015), with prevalence of symptoms of depression and anxiety around 22% and 35% respectively (Neuendorf et al., 2016). Utilising self-report assessment, lifetime prevalence of depression and anxiety has been found to be about twice as high in IBD patients as in the general population (Walker et al., 2008). The aetiology of mood disorders in IBD appears to be multifactorial, with complex "brain-gut" interactions (Alarhayem et al., 2015). Studies typically report higher levels of depression and anxiety for those who have active disease compared to those in remission (Calvet et al., 2006, Ben et al., 2012, Gandhi et al., 2014, Panara et al., 2014). It is suggested that the symptomatic phase of IBD is associated with increased depression and anxiety together with increased intestinal expression of inflammatory cytokines. This supports the hypothesis that raised inflammatory cytokines may be responsible for the increased risk of

depression and/or anxiety-related symptoms (Martin-Subero et al., 2016, Abautret-Daly et al., 2017). Furthermore, anti-TNF (Horst et al., 2015) and vedolizumab (Stevens et al., 2017) therapy have been found to lead to a reduction in disease activity scores and psychological symptom scores in patients with IBD. Conversely, patients on corticosteroids are more likely to experience adverse psychiatric effects (Fardet et al., 2007).

Overall psychological disturbances have been associated with poor coping, more disease flare-ups and non-adherence to medication (Goodhand et al., 2012, 2013). Likewise, depression and anxiety are associated with decreased health related QoL in IBD patients (Hyphantis et al., 2010, Iglesias-Rey et al., 2014). However, to date less than 40% of IBD patients with high levels of psychological comorbidities receive treatment for these mental health disorders (Evertsz et al., 2012). As of 2014, only 24% of IBD services in the UK have access to a dedicated clinical psychologist (IBD Standards Working Group, 2013). Existing models of care for IBD rarely specifically address the psychosocial aspects of the disease, typically operating within the biomedical model, where physical and psychological services are run independently of each other rather than being integrated into comprehensive care to recognise the complex patient needs (Mikocka - Walus et al., 2009, 2014).

1.1.9 Implications for treatment of IBD

Looking at data from large surveys in IBD, the most important treatment objectives from the patient perspective have been found to be improving QoL (40.2%) and completely resolving the symptoms (33.3%), followed by avoiding surgery, preventing relapses, and avoiding stomas (20.5%) (Casellas et al., 2016). Overall, patients' main expectation was for symptoms to be relieved by the treatment (Casellas et al., 2014). However, to assess the primary treatment objectives in IBD clinical trials, clinical or endoscopic indices are usually used and measures of QoL and symptom resolution based on patient reported outcomes are rarely considered (Hindryckx et al., 2015). In order to make treatment more effective it is therefore important to reconcile patient and clinician priorities.

As IBD has an early life onset, a chronic nature and does not generally shorten lifespan, addressing how patients deal with their disease is an important aspect of care (Graff et al., 2009). Indeed, in line with the international expert consensus of the recent Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative (Peyrin-Biroulet et al., 2015) on appropriate evidence-based treatment targets for IBD, the ultimate goal of treatment is not only to achieve endoscopic remission but also to improve patients' QoL. Manifestation of IBD cannot be fully accounted for by pathophysiology and it is important to have a biopsychosocial understanding of

illness where clinical outcome and disease exacerbation influence, and are strongly influenced by both biological and psychosocial factors (Bonaz and Bernstein, 2013). The simple management of inflammation does not necessarily impact upon the symptoms prioritised by the patients. As such, health-care professionals (HCPs) managing patients with IBD should aim to evaluate patient reported outcomes such as QoL, fatigue, work productivity, anxiety and depression, with the ultimate goal of improving patients' lives (Williet et al., 2016).

1.2 Fatigue in inflammatory bowel disease

In addition to diarrhoea, IBD burdens patients with a number of other symptoms (Singh et al., 2011b). The main symptoms that most patients consider to be a priority are: abdominal pain, bowel movement urgency and diarrhoea, fatigue, rectal bleeding and IBS symptoms of pain, constipation and bloating (Casellas et al., 2016). Fatigue is the third most predominant concern for patients with IBD, experienced by 44- 86% of patients with active disease and 22-41% of patients in remission (Czuber-Dochan, 2013a). The IBD priority setting partnership between the James Lind Alliance and the British Society of Gastroenterology (<http://www.jla.nihr.ac.uk/priority-setting-partnerships/inflammatory-bowel-disease>) (Hart et al., 2016) has therefore highlighted IBD fatigue as a top 10 UK research priority. Likewise, the development of fatigue management interventions has been identified as one of the top five research priorities in IBD nursing research in Europe (Dibley et al., 2017). Fatigue can have a significant negative impact on patients' QoL (Cohen et al., 2014, Kappelman et al., 2014, Minderhoud et al., 2007, Norton et al., 2015). Symptoms of fatigue limit individuals in their everyday lives, both physically and socially (Beck et al., 2013). Although fatigue understandably increases during periods of inflammation, for some patients it persists when disease is in clinical and endoscopic remission (Kreijne et al., 2015).

1.2.1 Definitions and assessment of IBD-fatigue

An accepted and sufficiently accurate definition of fatigue would be the first step towards achieving the further aims of detecting fatigue and increasing the available means of managing it. However, so far such definitions have proven elusive (Shen et al., 2006). Fatigue is often experienced in the general population (van't Leven et al., 2010); it is usually transient and can be caused by a lack of sleep or high stress levels (Kant et al., 2003). In patients with chronic conditions fatigue is a complex, multifactorial and multidimensional phenomenon, which has been described as a persistent overwhelming sense of tiredness, weakness, or exhaustion (Dittner et al., 2004), that can be mental, physical or both (Arnett and Clark, 2012). Unlike everyday tiredness, fatigue is often unrelieved by adequate sleep or rest (Cella et al., 1998).

Despite the pervasiveness of fatigue as a chief complaint in IBD patients, it is often only identified and treated in a relatively small proportion of those affected. Several factors may contribute to this tendency. Fatigue is typically underreported and IBD patients who do report fatigue symptoms often feel unsupported, with their reports of fatigue being ignored (Czuber-Dochan et al., 2013b). Fatigue is ultimately a subjective experience, and thus difficult to measure (Dittner et al., 2004). There is no objective ‘gold standard’ to measure fatigue (Shen et al., 2006). In a systematic review of the literature looking at fatigue in IBD (Czuber-Dochan et al., 2013a), the 18 studies included in the review attempted to measure fatigue utilising nine different scales, with many employing more than one scale. The Multidimensional Fatigue Inventory (MFI) and the Fatigue Impact Scale were the most frequently utilised scales. However, no rationale for using these was provided by study authors and both these assessment scales were developed in other chronic conditions and not specifically for patients with IBD. To date, only one scale, the Inflammatory Bowel Disease-Fatigue (IBD-F) has been developed and psychometrically tested specifically for this population (Czuber-Dochan et al., 2014a). Although it has been tested in only one study so far, condition specific tools reflect the needs and problems identified by patients themselves thereby potentially making findings more applicable to clinical practice (Norton et al., 2015).

1.2.2 Impact of fatigue on patients’ life

Although people with IBD report higher levels of fatigue when their disease is active, people describe struggling with fatigue even when in remission (Matini and Ogden, 2016). In a large scale European survey (Lönnfors et al., 2014), 50% of the respondents felt tired every day of the week during their last or current flare-up, and 95% at least one day a week. Between flare-ups, 83% of respondents felt tired at least one day a week, 20% daily. Likewise, fatigue was the most common reason for being absent from work due to IBD. Fatigue can have a negative impact on the personal and social life, on the work and employment and the ability to think clearly of people with IBD. People report limiting or missing activities, social events and travel due to their fatigue (Czuber-Dochan et al., 2013b). They also have to put their life on hold and cancel holidays (Schoultz et al., 2016). Ultimately, fatigue can lead people to give up hobbies and activities completely. As people feel tired, they lose their willingness to go out and socialise with others (Wilburn et al., 2017). This can result in them being isolated with very little energy to form or keep up relationships (Schoultz et al., 2016). Fatigue has also been associated with impaired sexual activity, including both sexual function and desire (Rivière et al., 2017). At home people with IBD-fatigue can depend heavily on family support and at work they often require short breaks or naps in order to get them through the day. Their lack of energy can also influence their decision-making. For instance some people report deciding not to have any more children for the feeling of not being able to parent properly. For others their fatigue influences their decision not

to work, take an early retirement or change jobs. Additionally, fatigue can cause people to make mistakes both at work and in their personal lives and to struggle to cope with parental responsibility (Czuber-Dochan et al., 2013b). Indeed, some people report not being able to think as clearly and sharply as they wanted to a lot of the time (Woodward et al., 2016).

Fatigue can impact people in different ways. For children and adolescents with IBD, fatigue can lead them to perceive themselves negatively, different to their peers. Their involvement with friends can lessen because of symptoms of fatigue (Nicholas et al., 2007). They also report absences from school during flares due to their fatigue (Devlen et al., 2014). Moreover, young people with IBD may feel compelled to disclose their illness to their friends due to a change in their social behaviour. Indeed, their lack of energy may result in a change in their behaviour that could not be otherwise explained (Barned et al., 2016). Women report feeling significantly more concerned by symptoms of fatigue compared to men (Pittet et al., 2017). For women with IBD, fatigue can limit them in their everyday life, socially, physically and at work. Fatigue makes it difficult to maintain the same level of social life as previously, hence often leading them to reduce their social networks to the closest family and friends. In terms of physical limitations, fatigue can contribute to women deliberately choosing not to exercise and avoiding physical housework activities such as cleaning and gardening. Women report concentration to be an essential problem which affects their work efficiency and their choice of tasks. Ultimately, fatigue can lead to feelings of anger, frustration, sadness, self-pity, worry, and grief. Furthermore, fatigue is often connected with feelings of a guilty conscience and powerlessness (Beck et al., 2013).

In addition to causing distress as a symptom itself, people's distress also stems from their perception that their fatigue is not taken seriously by HCPs (Czuber-Dochan et al. 2013b). People rarely have the opportunity to talk to their HCPs about their fatigue and during consultations the focus is mostly on bowel functioning and not on the impact of IBD on their QoL. Indeed patients report that they are made to feel as if their fatigue had to be accepted as an inevitable aspect of their IBD and there was nothing that could be done to change it (Czuber-Dochan et al. 2013b). People perceive that their fatigue is under estimated and no strategies to manage fatigue are offered by the UK National Health Service (NHS). Consequently, some report that NHS care would be improved by a holistic approach which incorporates also non bowel-related symptoms such as fatigue (Schoultz et al., 2016).

Chapter 2

2. Critical analysis of methodology

This chapter presents the methodology of this PhD project. An overall rationale for the study and the research questions that have been addressed is presented. A background on the current status in the methodology of complex interventions is subsequently provided. This sets the scene, explaining how the PhD project fits within the current field of complex intervention development. By purposively explicating known strengths and limitations in complex intervention design, the first part of this chapter justifies how the design of the PhD intervention resulted from an attempt to build upon these strengths and overcome these limitations. Subsequently, the second part of this chapter outlines the practical application of this knowledge to the methodological design of the study phases. As this is a methodology chapter and not a methods chapter, the specific methods of each phase of the study are not presented here but are described in the Methods section of each of the published four papers. As word count constraints imposed by published journals prevents an exhaustive explanation of the study processes, a more detailed account of the methods involved in each phase, together with justifications for their choice is presented at the end of each of the published papers. The intervention development process is presented at the beginning of Chapter 5, prior to the intervention protocol, published as Paper 3.

2.1 Rationale for the study

Evidence presented in Chapter 1 demonstrates that fatigue is a prevalent and predominant concern in patients with IBD and it has a significant impact on patients' QoL. The aetiology of fatigue is not well understood by patients or HCPs, with evident implications for its management. To date interventions for IBD-fatigue are scarce, demonstrating limited short-term or no benefit, and have not been implemented into clinical practice. The development of a robust theoretically-driven intervention to improve fatigue is therefore a primary concern for this population.

The overall aim of the study was to develop a complex intervention for the management of fatigue and test its feasibility and potential efficacy in patients with IBD. To achieve the overall study aim, a series of questions were posed.

2.2 Research questions

- Which potentially modifiable physical and psychosocial factors are associated with fatigue in patients with IBD?
- Which available interventions for the management of fatigue have been identified and previously tested in patients with IBD?

- Which mechanisms of change are relevant, acceptable and useful when developing an intervention for the management of fatigue to patients with IBD?
- What is the feasibility of an intervention for the management of fatigue in patients with IBD?
- What is the feasibility of a trial protocol for delivering a full pragmatic randomised controlled trial (RCT) of an intervention for the management of fatigue in patients with IBD?
- What are the initial estimates of efficacy of an intervention for the management of fatigue in patients with IBD?

2.3 Methodological rigour in intervention development

Although the importance of methodological rigour at the early stage of intervention development is now widely recognised (Craig et al., 2008), it has been suggested that there is continuous waste of research by developing interventions that never impact on healthcare (Chalmers et al., 2014). Much healthcare research is currently wasted because findings are unusable by clinicians for patients' care (Glasziou et al., 2008, Chalmers and Glasziou, 2009) or to inform public health policy (Ahmad et al., 2010). Interventions shown to be efficacious at the trial stage, often prove to have diminished effectiveness when disseminated into the real world (Glasgow et al., 2012). Similarly, findings from studies that could be important for clinical practice are subsequently found impossible to replicate (Glasziou et al., 2008). This could signify suboptimal health outcome, poor return on investment and significant opportunity costs (Neta et al., 2015).

The potential reasons that could explain these phenomena may relate to: a scarcity of interventions based on theories (Michie et al., 2005), a limited understanding of the causal assumptions about how interventions work (Moore et al., 2015), an inadequate reporting of intervention development (Hoffmann et al., 2014b, Hoddinott, 2015), and an insufficient use of intervention development frameworks for the development, testing, evaluation and implementation of interventions (Campbell et al., 2000). Summary of these problems and how they were overcome in this PhD project design in order to improve methodological rigour is summarised in Table 1 and further explained in this chapter.

Table 1: Issues compromising methodological rigour and proposed resolutions for the methodological design of the intervention.

Identified problem	Proposed solution
2.3.1 Scarcity of interventions based on theories	Use of theory in intervention development
2.3.2 Limited understanding of the causal assumptions about how interventions work	Use of logic models
2.3.3 Inadequate reporting of intervention development	Use of reporting guidelines to report intervention development
2.3.4 Insufficient use of intervention development frameworks	Use of an intervention development framework

2.3.1 Theory in interventions

A theory is defined as a coherent and non-contradictory set of statements, concepts, or ideas that organises, predicts, and explains phenomena, events, and behaviour. Theories are useful in intervention development because they specify determinants of behaviour that are potentially amenable to change. Thus, theories inform us which variables should be targeted by interventions, namely – which variables should be manipulated in order to produce the desired change in behaviour (Eccles et al., 2005). The application of theory is advocated as an integral step in intervention design and evaluation and in evidence synthesis (Davis et al., 2015). The development of interventions should be informed by a theory, and both intervention development and evaluation require a strong theoretical foundation with empirical support (Hardeman et al., 2005, Michie et al., 2005). The intentional testing of theory in research helps to expand the knowledge base (Johnston and Dixon, 2008). The use of theory may help to explain how the intervention works (Glasgow and Emmons, 2007). Development and evaluation of complex interventions is challenging as a result of problems in identifying and separately assessing the effects of various components of the intervention (Blackwood, 2006). As such, by utilising a theory in the development process, interventions may target specific mechanisms of change, facilitating an understanding of what works across different contexts and clinical populations (Michie et al., 2008). Furthermore, theoretically identified mechanisms of action can be investigated to gain further understanding of how the intervention brings about its effects (Michie and Abraham, 2004, Rothman et al., 2004). Addressing these issues may ultimately improve the translation of research into practice (Michie et al., 2011).

Specifically, the use of theory is recommended by the UK Medical Research Council (MRC) (Campbell et al., 2000) to provide hypotheses of specific mechanisms and interactions in complex interventions (Noar and Zimmerman, 2005, Siemonsma et al., 2010, Coryn et al., 2011) during the first phase of the development of interventions (Campbell et al., 2000). This is particularly useful in interventions for long-term conditions that encompass several interacting management

strategies, which are difficult to evaluate and reproduce (Tougas et al., 2015). Indeed, evidence from long-term conditions, including diabetes (Zhao et al., 2016), cancer (Avery et al., 2013) and acquired immune deficiency syndrome (Protogerou and Johnson, 2014) shows that trials making use of theory tend to have better medical and psychological outcomes than those that did not. The use of theory assisted in the identification of theoretical constructs to target in the intervention and which participants to include in the study (Ayling et al., 2015). It also enabled the measurement of theoretical constructs pre and post intervention, allowing researchers to determine the intervention's mechanism of action which can then help with further refinement of the theory (Michie and Prestwich, 2010).

Nonetheless, it is difficult to define 'use of theory' and 'theory informed' interventions, because 'theory-based' interventions could employ techniques that are not consistent with the underlying theory or use only parts of the theory. Furthermore, several reviews assessing the effect of the use of theory fail to consider how theory informed the intervention. These reviews only compare effect sizes between studies that explicitly report the theoretical grounding of the intervention versus those that do not. Guidelines for the transparent reporting of the use or non-use of theory would make it easier to unravel the extent of the problem. Overall, evidence regarding the association between the use of theory to develop interventions and resultant better outcomes is mixed (Prestwich et al., 2015). However, theory should still be used to aid in understanding complex mechanisms and interactions between components of interventions (Noar and Zimmerman, 2005, Siemonsma et al., 2010, Coryn et al., 2011).

There are multiple theories available to develop interventions. A recent scoping review of theories of behaviour and behaviour change (Davis et al., 2015) identified 82 theories spanning across a myriad of behaviours (*e.g.* increasing physical activity, safe sex practices, smoking cessation). Another systematic review of behavioural theories (Kwasnicka et al., 2016) identified 100 theories encompassing five main themes: motives, self-regulation, habits, resources and contextual factors. However, in the health behaviour literature (Davies et al., 2010, Glanz and Bishop, 2010, Prestwich et al., 2014, Davis et al., 2015), only some interventions describe using any theoretical framework or theory components to guide their development. The limited use of theory may be due to the fact that researchers do not consider the application of theory helpful or they may lack the skills to select or apply theory, especially given the lack of guidance in the area (Gainforth et al., 2015). Current recommendations to use theory early in the design of interventions do not specifically describe how to incorporate theory into the development process (Tougas et al., 2015). Moreover, there is heterogeneity in the distribution of frequency of, and approaches to, theory use (Davis et al., 2015). Processes by which theories are selected and the methods for measuring theoretical constructs are not well developed in the literature. Researchers

may “use” theory to varying degrees along a continuum, ranging from studies that are simply informed by theory, to those that apply or test theory more explicitly, to those that build and/or extend theory (Painter et al., 2008). More studies evaluating theory-based interventions are therefore required and encouraged (Avery et al., 2013). In order to overcome the limitations of interventions without a theoretical basis, theory was incorporated in the design of the PhD intervention. Further description of the chosen theory and the rationale for this choice is provided in *Section 2.6.3 Step 2b: Identifying the appropriate theory*.

2.3.2 *Logic models in interventions*

In addition to the use of theory in interventions, the UK MRC framework guidance for complex interventions (Moore et al., 2015) advises the use of logic models in order to clarify causal assumptions of the intervention. However, the use of logic models has only recently been recommended and is still relatively rare (Hawe, 2015). A logic model can be defined as a graphic description of a system designed to identify important elements and relationships within that system (Anderson et al., 2011). This includes a graphical representation of the pathways from problem to intervention or individual intervention components to anticipated outcomes (Rehfuess et al., 2017). Logic models can help to conceptualise and handle intervention design complexity by i) making underlying theories of change explicit, including assumptions about causal pathways between the intervention and multiple outcomes, ii) depicting intervention components and the relationships between them, and iii) displaying interactions between the intervention and the system, within which it is implemented (Rohwer et al., 2017). Logic models add to theories of change in that they are used to outline programme components and check whether they are plausible in relation to the outcomes; they do not require the underlying assumptions to be specified (Clark and Anderson, 2004). Indeed, although it is useful for interventions to draw explicitly on existing theories, sometimes an intervention development can be driven also by other factors such as experience or common sense. Logic models can therefore allow researchers to be clear about what these additional assumptions are and how they fit alongside the chosen theory of change (Moore et al., 2015). In order to further strengthen the intervention design, a logic model for the intervention was included in the PhD project. A description of the model is provided in *Section 2.6.4 Step 3: Modelling processes and outcomes* (Figure 6, p. 58).

2.3.3 *Reporting of interventions*

To comprehend the results of an RCT, its design conduct, analysis, and interpretation has to be understood by the reader. This goal can be achieved only through total transparency from authors (Moher et al., 2001). Guidelines and checklists help individuals meet certain standards by providing sets of rules or principles that guide towards the best behaviour in a particular area. They are successfully and routinely used, often on a compulsory basis, in many areas of human

activity to prevent errors and omissions. Reporting guidelines have been developed to provide structured advice on how to report research studies in order to improve the accuracy and transparency of publications. They complement advice on scientific writing and journals' instructions to authors, with some journals requiring the authors to adhere to the relevant selected guideline when submitting their manuscripts (Simera et al., 2010). In June 2008, the UK NHS provided funds to set up the EQUATOR (Enhancing the QUALity and Transparency Of health Research), an international initiative that promotes transparency and accurate reporting of health research studies. EQUATOR provides resources, education and training to facilitate good research reporting (Moher et al., 2008). Attempting to bring all available reporting guidelines under one roof to allow their easy identification and use, the EQUATOR website lists over 90 reporting guidelines developed with the objective of improving the reporting of research studies relating to health. However, there are major differences in the scope, content and development processes of individual guidelines and there is currently no available tool for the evaluation of reporting guidelines (Moher et al., 2009). Despite, the extensive availability of these guidelines, a systematic choice of a guideline taking into account its characteristics, development process and robustness in their use in the editorial process is therefore still difficult.

The two most utilised reporting guidelines for RCTs are the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher et al., 2001) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Chan et al., 2013). The CONSORT statement is an evidence-based minimum set of recommendations, consisting of a checklist, flow diagram and descriptive text, intended to facilitate the complete and transparent reporting of RCTs and subsequently aid in their critical appraisal and interpretation (Turner et al., 2012). Evidence suggests that use of the CONSORT guidelines is associated with an increase in the completeness of reporting of clinical trial full-texts (Turner et al., 2011, 2012) and abstracts (Mbuagbaw et al., 2014). The uptake of CONSORT is reflected in a number of metrics. Combined, the 1996 (Begg et al., 1996), 2001 (Moher et al., 2001) and 2010 (Schulz et al., 2010) publications of the CONSORT Statement and Explanation and Elaboration documents (Altman et al., 2001) have been cited more than 12,000 times (according to Scopus, May 2015), making CONSORT among the most highly cited biomedical publications of all time. Also an indicative measure of CONSORT uptake, is the support from major editorial organisations and its endorsement by more than 63% of high impact journals in medical specialties and general medicine (Shamseer et al., 2016). This includes a large group of rehabilitation medicine Editors who signed up collectively to mandate the use of reporting guidelines in their journals in 2014 (Chan et al., 2014b).

The SPIRIT checklist is a 33-item checklist of minimum recommended protocol items, which is intended to be used as a guide when preparing a protocol for a clinical trial. Similarly to CONSORT, the SPIRIT was developed to address unclear description of trial methodology in protocols (Chan et al., 2013). To date, a large number of groups have endorsed the SPIRIT 2013 Statement including more than 50 journals, academic institutions, industry, trial groups and patient groups (Sarkis-Onofre et al., 2015). Most recently, the Template for Intervention Description and Replication (TIDieR) initiative has also introduced a checklist extension to SPIRIT and CONSORT to help researchers to more fully describe interventions, with the ultimate aim of improving their replicability (Hoffmann et al., 2014c). The TIDieR guide acknowledges that providing complete intervention descriptions may increase the word count and offers suggestions for how authors may manage this, including providing details in published protocols and online supplementary materials – which 75% of journals now have the capacity to host (Hoffmann et al., 2014a). Indeed, the study protocol can provide detailed information that is not available in the main published text. Its availability can therefore help to clarify unclear reporting and identify selective reporting within publications, as well as inform clinical practice and future research (Wieseler et al., 2013).

Despite these promising findings relating to the use of reporting guidelines, adequate reporting of interventions is still not consistent across journals and the implementation of guidelines is still far from standardised (Shamseer et al., 2016). A systematic scoping review of adherence to reporting guidelines in healthcare literature reported that 43 of 50 reviews found that levels of adherence to reporting guidelines were suboptimal (Samaan et al., 2013). Likewise, a systematic review of studies investigating reporting improvements as a consequence of endorsement by journals of reporting guidelines other than CONSORT (Stevens et al., 2014), found that insufficient evidence exists to determine the relation between journals' endorsement of reporting guidelines and the completeness of reporting in published health research reports. As CONSORT is the most extensively used reporting guideline, this may suggest there could be a significant variation in reporting according to the chosen guideline. Indeed, there is still wide variability in the information contained on journal websites on what to include in reports of trial methods, especially in relation to the intervention used or details of participants (Moher et al., 2016). Published reports of interventions often remain brief and vague (Tate et al., 2016), and focus only on results (Riley et al., 2008, Hoffmann et al., 2014b), with important processes and decision-making in the early stages of intervention development being confined to grant proposals and PhD theses (Hoddinott, 2015). Some editors typically require only limited information on the theoretical basis of the intervention, and space constraints of published papers preclude a thorough description of the intervention components. When replicating or modifying existing interventions,

researchers and practitioners are therefore sometimes left guessing about the key components that made an intervention successful or unsuccessful (Tate et al., 2016).

Additionally, despite their importance, protocols are not always publicly accessible (Chan et al., 2014a). Some fields, such as psychology, document standardised interventions in treatment manuals. Treatment manuals describe the intervention theory, goals, and strategies, including how a programme should be organised and delivered, and the role and responsibilities of interventionists (Bond et al., 2000). However, a recent review of non-pharmacological RCTs found that such materials are infrequently (47%) published (Hoffmann et al., 2013). Alternatively, even when intervention manuals are available they vary greatly in the level of detail and style (Michie and Abraham, 2008). When interventions are complex, indicating they are built up from a number of components which may act both independently and interdependently (Campbell et al., 2000), reporting of intervention development involves more than enumerating a list of ingredients. The components, frequency, monitoring and mode of delivery may all influence efficacy. Thus, for research to be replicated and reliability adopted by HCPs and patients, a detailed description of the decision-making processes and a justification for the inclusion of each component of the intervention according to theoretically predicted mechanisms of action should be provided. Not only should the description of the intervention elucidate what works, but also how and ultimately why the intervention components interact to achieve the proposed change (Michie et al., 2011, Hoffmann et al., 2013, 2014b). In order to overcome limitations in intervention reporting, the protocol of the intervention was published (Artom et al., 2017; Paper 3) and a justification of the inclusion of the intervention components following a framework for the development of complex interventions is described in *Section 2.5 Application of the MRC framework to this PhD project*.

2.3.4 Intervention development frameworks

Having identified the relevant components of the intervention using a theory, the next step is to develop an appropriate intervention. Indeed, problems often arise in the evaluation and implementation of complex interventions because researchers have not fully defined and developed the intervention (Campbell et al., 2000). The use of an intervention development framework can aid in this process. Frameworks are systems of concepts, assumptions, and theories organised graphically or narratively (Eccles et al., 2005) and in the context of unexplained heterogeneity of outcomes of trials of complex interventions, thorough attention to the different phases of intervention development can help researchers consider the causal assumptions of their intervention before initiating an RCT (Jonkman et al., 2017). However, not many intervention development frameworks have been published and confusion remains as to which framework to follow and which intervention development methods are more likely to be

most suitable for different types of interventions (Levati et al., 2016). As such, intervention development frameworks are not always used and definitive RCTs of complex interventions do not always undergo all the phases of development. Interventions are built instead on investigator's interpretation of other empirical studies (Grimshaw et al., 2005).

Developing an intervention without an intervention development framework is akin to exploring the clinical role of a drug, without understanding its pharmacology, the physiology of the patient being treated or the pathophysiology of the patients' problem. It could be argued that this is an expensive version of trial-and-error with no system in place to anticipate success of the intervention and a low likelihood of being able to replicate the success of the intervention, if it is achieved (Eccles et al., 2005). Although going through the phases of a framework may seem like a lengthy and costly process, early observational and piloting studies require significantly less resources compared to the cost of multi-centre RCTs (Sturt et al., 2006). Full-scale trials may provide convincing evidence for the introduction of interventions in clinical practice. Ultimately, however, the interventions may prove to be inadequately prepared to be implemented in real-world healthcare systems (Rowlands et al., 2005). In order to overcome the limitations of developing complex interventions without an intervention development framework, the development of the PhD intervention was guided by the use of a framework for complex interventions. Further description of the justification for the choice of the framework is described in *Sections 2.4.4 and 2.4.5*, further explanation of its application to this PhD project is described in *Section 2.5. Application of the MRC framework to this PhD project*.

2.4 The Medical Research Council Framework for the development of complex interventions

2.4.1 First version of the MRC framework

The MRC framework was firstly published in 2000 (Campbell et al., 2000). This guidance was published in response to the difficulties faced by those attempting to develop multiple-component interventions and evaluate their impact (Datta and Petticrew, 2013). The first version (Figure 3) of the MRC framework (Campbell et al., 2000) presented a step-wise approach in five phases: pre-clinical (theory), modelling, exploratory, definitive RCT and long-term implementation phases. The *pre-clinical (theory)* phase aims to explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues. Evidence from the literature should be explored, for instance this may take the form of a review. It may also involve qualitative testing using interviews, surveys or observational studies with patients, HCPs and stakeholders about the studied problem. The *modelling* phase aims to identify the components of the intervention, how they fit together and the underlying mechanisms by which they will influence outcomes. The *exploratory* phase is where the evidence gathered thus

far is put to the test, the recruitment procedures and intervention itself are piloted in practice, and the suitability of the outcome measures is assessed. Based on the results of the *exploratory* phase, a definitive RCT then evaluates the effectiveness of the complex intervention. This is then evaluated in the process *evaluation* phase, in order to explain discrepancies between expected and observed outcomes in the real world, to understand how context influences outcomes, and to provide insights to aid implementation of the intervention into clinical practice.

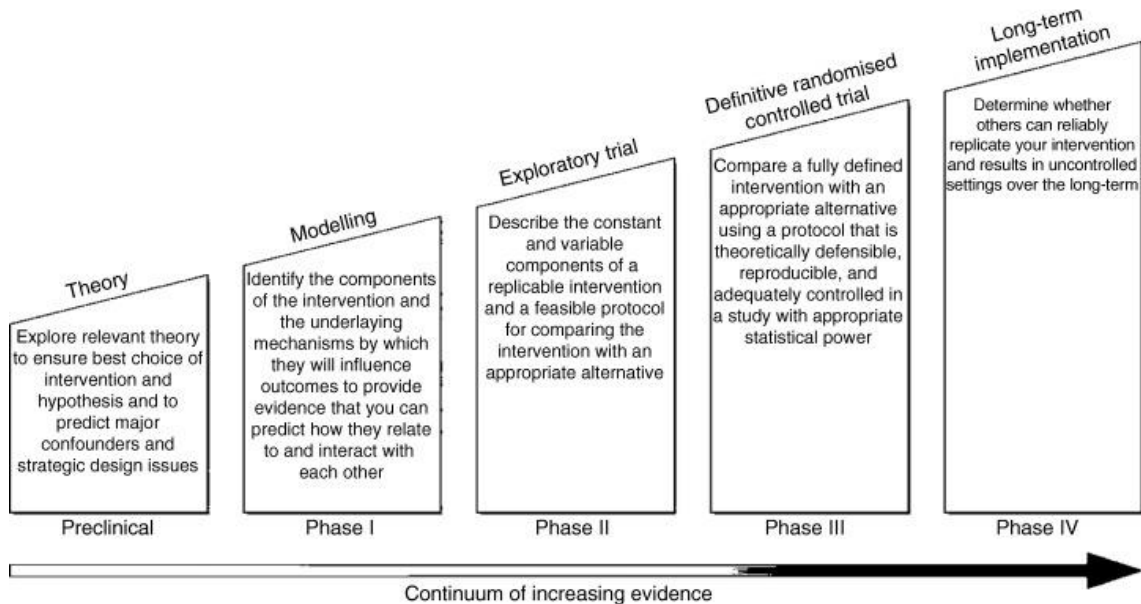


Figure 3: Original Medical Research Council Framework for the development of complex interventions (Campbell et al. 2000).

Despite its usefulness, the first version of the framework was criticised for a number of reasons including: neglecting the early phases of development and modelling work (Hardeman et al., 2005), adopting a linear model of evaluation process and omitting to consider the context of the intervention when assessing efficacy in RCTs (Campbell et al., 2007). Firstly, although the 2000 framework emphasises the importance of the phases of development and modelling, it lacks details on how these phases should be conducted (Hardeman et al., 2005). Specifically, researchers may encounter challenges when theories do not exist to guide intervention development or where the evidence or theory underpinning the intervention may need to be refined through the modelling phase itself (Corry et al., 2013). Secondly, using a linear stepwise approach, where phases of the intervention development are conducted sequentially, may not neatly lend itself to complex interventions involving multiple components and methods of enquiry. Indeed, in complex interventions there may be an overlap in certain processes, making it difficult to pre-determine a set order of phases (Massoud et al., 2016). Finally, the context of the intervention cannot be omitted. Understanding context is crucial both when designing interventions and when assessing whether an intervention that was effective in one setting might work in others. The context includes the wider socio-economic background, the health service

system, the characteristics of the population, the prevalence or severity of the condition studied and how these change over time. If the context is not taken into account, it is difficult to determine whether it is the intervention that did not work or whether it was applied to an inappropriate context (Craig and Petticrew, 2013, Campbell et al., 2007). The MRC framework in its 2000 version advocates the use of RCTs as the primary method of enquiry. RCTs assess the efficacy of interventions within a particular context. By advocating the use of RCTs as a gold standard, the framework thus fails to determine whether outcomes would be transferrable and effective in other contexts outside the ones defined by the RCT (Blackwood et al., 2010).

2.4.2 Second version of the MRC framework

An updated version of the MRC framework (Figure 4), aiming to address previous limitations was published in 2008 (Craig et al., 2008). Attempting to address the issue of linearity, the 2008 framework has a more flexible approach and conducts the first three phases simultaneously in an iterative process, to better understand the problem, the intervention and the evaluation (Massoud et al., 2016). Nonetheless, an order in the phases is still suggested. For instance, modeling and pilot testing of the intervention, should still precede the evaluation phase, to ensure the intervention has been developed to a point where it is expected to have a worthwhile effect and where the mechanisms by which this effect is generated are reasonably understood (Haji et al., 2014). Likewise, in effort to resolve the issue of context, the new version of the framework proposed to supplement RCTs with other methodological approaches, including the use of qualitative research strategies (Blackwood et al., 2010). Qualitative strategies, utilised at various phases of the framework can help understand the role of contextual factors in producing outcomes (Nelson et al., 2015).

Broadening its conceptualisation of complexity, the new version of the MRC framework conceptualises it as: i) the number of interacting components within the experimental and control interventions, ii) the number and difficulty of behaviours required by those delivering or receiving the intervention, iii) the number of groups or organisational levels targeted by the intervention, iv) the number and variability of outcomes, and v) the degree of flexibility or tailoring of the intervention permitted (Noyes et al., 2013). The framework therefore aims to guide researchers through these aspects of complexity in order to more effectively design and evaluate complex interventions (Blackwood et al., 2010).

The updated MRC framework includes four phases: development, feasibility and piloting, evaluation and implementation. The current version of the MRC framework advises an iterative, stepped, structured and mixed-method approach rather than a linear approach. The intervention *development* phase of the framework involves the development of the intervention's theoretical

rationale. This phase aims to identify underpinning active ingredients and how these are expected to interact with one another and with the context of delivery to generate outcomes. It includes identifying the evidence-base, identifying or developing theory, and modelling processes and outcomes. The *feasibility and piloting* phase includes testing the feasibility and acceptability of the proposed intervention and its evaluation methods. Further refinements may be made to the intervention theory after this phase to optimise the intervention design, logic model and the proposed evaluation design prior to testing effectiveness and cost-effectiveness. Once a well-theorised intervention has been developed and feasibility questions addressed, RCTs are recommended in the *evaluation* phase to examine their effectiveness (and cost-effectiveness) whenever randomisation is practicable. Finally, in the *implementation* phase, studies are needed to address the scale-up of interventions into routine practice and whether they are still effective in the real world. The cumulative effect of these processes should be the generation of a strong theoretically-grounded intervention, providing greater confidence that outcomes observed during trials can be replicated in real-world settings, and which supports the ongoing cycle of developing and evaluation of complex interventions (Blackwood et al., 2010, Bonell et al., 2014, Fletcher et al., 2016).

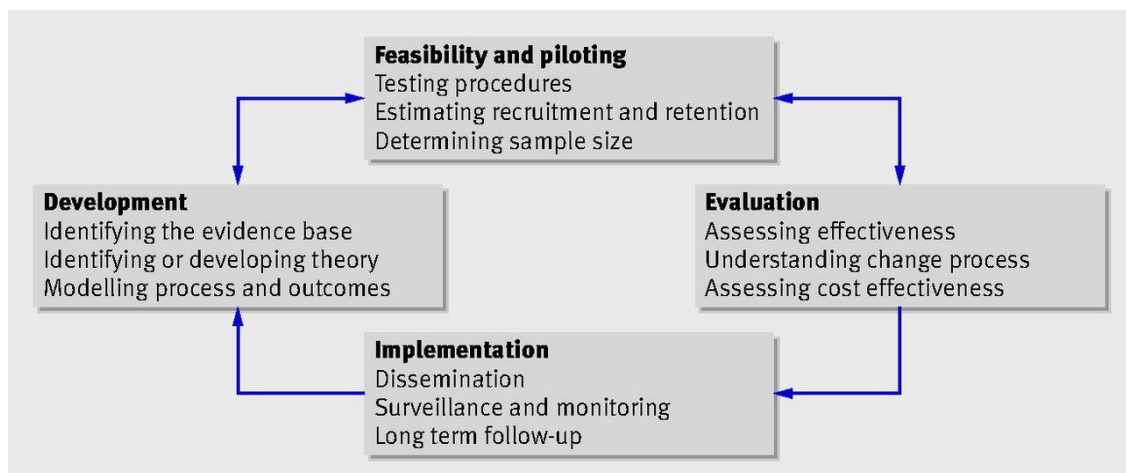


Figure 4: Revised Medical Research Council Framework for the development of complex interventions (Craig et al. 2008).

2.4.3 Ongoing limitations of the MRC framework

Despite the MRC framework's refined version published in 2008 (Craig et al., 2008), it is still not without limitations. The main criticism remains around the issue of context. Although the new version of the framework takes context more into account, questions remain concerning the demonstration of efficacy and effectiveness. The MRC in its 2008 version still makes no mention of considerations of context when discussing intervention development, and only brief mention of the role of contextual factors in modifying intervention's effects (Moore and Evans, 2017). It is unclear if the health evaluation research should be studying the effect of the intervention per

se, or the contextual factors that promote or inhibit its effectiveness, or both. While the MRC acknowledges that trials on their own may not be able to provide comprehensively definitive information, it still maintains the traditional assumption that interventions work or do not work based on their inherent quality, notwithstanding the context in which they are operationalised. There is thus the assumption that the reliability of the intervention is the key factor in its success or failure in everyday settings (Blackwood et al., 2010). Furthermore, the MRC's definition of complexity (*i.e.* including several components), may not take context enough into account and may therefore be criticised for not necessarily being comprehensive. Indeed, it can be claimed that complexity is a characteristic of the system within which an intervention acts as well as being an inherent characteristic of an intervention itself.

The issue of overlooking context is particularly relevant in the *implementation* phase of the MRC framework. The effectiveness of complex interventions, together with their success in reaching all its target populations, is significantly influenced by their implementation in a given context (Waters et al., 2011, Wells et al., 2012). Understanding whether such an intervention really makes a difference requires a conceptualisation of the intervention within its context of implementation (Pfadenhauer et al., 2017). Implementers of interventions are challenged by two conflicting demands: on the one hand, universal interventions are to be implemented with fidelity, on the other hand, these must be adapted to local needs and circumstances (Shortell et al., 2004). If interventions are conceptualised as attempts to disrupt mechanisms which perpetuate and sustain a problem in a given time and place, they cannot be understood in isolation from the systems whose functioning they attempt to change. Stakeholders therefore need to be continually involved in the development of complex interventions through intervention coproduction, ensuring that pertinent contextual influences can be sufficiently accommodated within theories of change, and that theories still retain their integrity in light of this context (Moore and Evans, 2017). In order to overcome the issue of overlooking context stakeholders, both patients and HCPs were involved throughout all stages of the intervention development and piloting. Further description of how this involvement was conducted is provided in *Section 2.6.4 Modelling processes and outcomes* and *Section 2.7.1 Testing procedures*.

2.4.4 Comparing the MRC framework with other intervention development frameworks

The main intervention development frameworks preceding the year 2000 included: Intervention Mapping (IM; Bartholomew et al., 1998), the PRECEDE-PROCEED model (Green and Kreuter, 1999) and the RE-AIM framework (Glasgow et al., 1999). However, they tended to be oriented towards an individual behaviour change, provided little specific detail on intervention development or required great technical skills and resources (Wight et al., 2015). The PRECEDE-PROCEED model, for instance, specified phases of needs assessment that mapped onto the first

phase of the MRC framework yet it does not cover the successive steps of modelling and piloting which are required to obtain the finished intervention product. Furthermore, despite providing a framework for programming behavioural changes, these changes may not be as straightforward when applied to symptom management in long-term conditions (Hardeman et al., 2005). Although useful, the RE-AIM framework is an evaluation model not an intervention development model (Glasgow et al., 1999). It hence focuses on phases 3 to 5 of the MRC framework (Hardeman et al., 2005), which go beyond the scope of the PhD project.

Of the above frameworks, IM was possibly the most fitting for the needs of this project. IM was innovative at its advent as it provided a system for the integration of theory, empirical findings from the literature, and information from the target population in a systematic way. It has a visual component, including diagrams and matrices and iterative steps. Each step requires performance of several specific tasks leading to a product that provides the basis for the subsequent steps. The five key steps of the IM process are: i) creating matrices of proximal programme objectives from performance objectives and determinants of behaviour and environmental conditions, ii) selecting theory-based intervention methods and practical strategies, iii) designing and organising programmes, iv) specifying adoption and implementation plans, and v) generating an evaluation plan. IM originated in response to questions on how to use theory in intervention development (Kok et al., 2016). The MRC framework has been criticised for not providing detailed guidance on designing an implementation intervention (French et al., 2012). Some have therefore utilised the detailed guidance provided by IM in order to fulfil the criteria stipulated by the framework (Taylor et al., 2013). However, the creation of the matrices of change objectives can be time-consuming and at times the information requires a large amount of reviewing, revising and refining (Pittson and Wallace¹, 2011). For this reason, IM is typically applied to unidimensional behaviours, such as weight gain prevention and physical activity modification (Kwak et al., 2007). Moreover, IM originated in primary care prevention (van Oostrom et al., 2007). Its use was therefore deemed inappropriate to guide the development of an intervention addressing a multidimensional and multifactorial symptom like fatigue.

2.4.5 Rationale for choosing the MRC framework for this PhD project

To date the MRC framework is the most widely used guideline for the development of complex interventions (Corry et al., 2013). In a systematic review aiming to identify guidelines for intervention development and to examine how researchers have used guidelines when developing interventions (Corry et al., 2013), the only guideline reported to have been used in the development of interventions is the MRC framework with 9 of 14 papers that describe the development of an intervention reporting the use of this guideline. Five papers reporting the development of interventions did not refer to the MRC framework or specify the use of any other

framework to guide the development of the intervention. Similarly, in a UK scoping review aiming to identify and synthesise the available evidence relating to strategies and methods utilised to optimise complex interventions at the pre-trial stage (Levati et al., 2016), 17 of the 27 studies used the MRC framework. The studies used the 2000 framework, the updated 2008 version or a combination of the two. Conversely, the use of other frameworks is rare and heterogeneous, with no other framework utilised consistently for the development of complex health interventions.

The choice of the MRC framework has likely become popular as its strength lies in its emphasis on modelling complex interventions based on theory, pilot testing active ingredients, and the iterative nature of the research process, which are essential in developing complex interventions (Haji et al., 2014). Although it does not guarantee success, the MRC framework sets standards for theoretical and methodological development within an RCT that could ultimately improve the intervention and it proposes developing the best intervention and the best evaluation methods at each step (Reelick, 2011, Redfern et al., 2006). The aim of the guidance was to draw attention to methods which are known to work, and make recommendations that could be supported by practical examples (Craig and Petticrew, 2013). In both its versions the MRC framework is clearly not perfect but there are currently no other frameworks for the development of complex interventions which provide such comprehensive, yet flexible guidance for researchers. For example, identifying the evidence base can help to ensure that the best choices are made regarding the intervention and proposed hypothesis, and highlights strategic design issues. The identification or development of the appropriate theory may lead to changes in the hypothesis and the identification of potentially useful structural organisations or components of the intervention prior to its development. Modelling may identify the potential vulnerabilities of an intervention and by testing out processes and outcomes researchers can overcome these vulnerabilities before a large-scale RCT (Reelick, 2011). In conclusion, whilst taking its limitations into account, it was therefore decided to utilise the MRC framework to guide this PhD project.

2.5 Application of the MRC framework to this PhD project

This PhD project stems from a body of work related to fatigue in inflammatory bowel disease (IBD) developed by researchers at King's College London, University College London and Addenbrookes' NHS Trust. A large, four-year study, conducted for Crohn's and Colitis United Kingdom (CCUK) charity and funded by the Big Lottery Fund was undertaken between 2010 and 2014. The project set out to examine the causes and nature of fatigue, pilot a fatigue assessment tool and explore interventions to improve its management in IBD. Prior to the beginning of this PhD project, the research team already completed: interviews with patients about their experience and management of IBD-fatigue (Czuber-Dochan et al., 2013b), interviews with HCPs to explore

their perceptions of IBD-fatigue and its impact on everyday life of people with IBD (Czuber-Dochan et al., 2014b), a review of description and management of IBD-fatigue (Czuber-Dochan et al., 2013a) and the development (Czuber-Dochan et al., 2014a) and testing (Norton et al., 2015) of an IBD-specific fatigue assessment tool. An in-depth description of this work is beyond the scope of this chapter. However, the completion of these studies was crucial to the development of this PhD and it should therefore be taken into account when evaluating the choices made in this PhD. Specifically, in the first step of the process (identifying existing evidence), the bulk of knowledge about fatigue produced by these previous studies by members of the supervisory team made a significant contribution in shaping the starting point of this PhD. A clear distinction will be made between the work already completed prior to this PhD, the work that forms part of this PhD (Figure 5) and the work that will follow the completion of this PhD project.

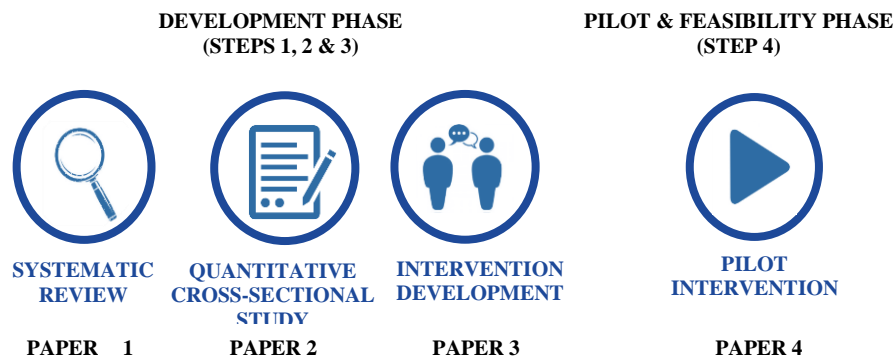


Figure 5: Overview of PhD project phases.

Due to the previously discussed limitations of the first version of the MRC framework (Campbell et al., 2000), the second version of the framework was utilised to guide this PhD project. The revised version of the MRC framework (Craig et al., 2008) characterises the process of development through to implementation in phases which do not necessarily follow a linear sequence. This PhD project covers the first two phases: the *development* phase and the *feasibility and piloting* phase (Figure 5). Although, not strictly defined this way in the MRC framework original document, for the purpose of clarity, each phase has been sub-divided into steps. Utilising the MRC guidance as a starting point, the application of each step of the process to this PhD has been described in detail in this chapter. This included: the specific project aims associated with each step, the research questions answered by each step, the research methods chosen to answer the research questions in each step, the publication output/s associated with each step and the ways in which the outcomes produced by each step informed the other steps of the research process (Table 2).

As this is a Methodology chapter, full results of the study steps will not be presented here. Results will be in the Results sections of the individual published papers. Only results which are relevant in feeding in to the next step of intervention development are reported. As the MRC framework has been criticised for sometimes lacking detailed direction on the design process (French et al., 2012), when gaps in the framework guidance were identified, an effort was made to integrate it with information from other resources that could be of use. In order to guarantee transparency and allow for better development of future interventions, where issues with utilising the MRC framework to guide the development process that could not be resolved, these were highlighted and further discussed in the Discussion chapter of this PhD thesis.

Table 2: Contribution of the stages of the MRC framework to the development of the intervention.

MRC steps	DEVELOPMENT PHASE			FEASIBILITY AND PILOTING PHASE
	Step 1: Identifying the evidence-base	Step 2 a & b: Identifying components of the intervention and identifying appropriate theory	Step 3: Modelling processes and outcomes	Step 4: Testing procedures and estimating recruitment and retention
Aims	-To identify the evidence-base on interventions for fatigue in IBD	-To use the theory to identify components of the intervention -To identify an appropriate underlying theory for the development of an intervention for fatigue in IBD	- To use patient and HCPs perspectives to inform the adaptation of an intervention for MS-fatigue to IBD-fatigue	- To test procedures of an intervention for the management of fatigue in patients with IBD - To estimate recruitment and retention of an intervention for the management of fatigue in patients with IBD
Research questions	-Which available interventions for the management of fatigue have been identified and previously tested in patients with IBD? -Which potentially modifiable physical and psychosocial factors are associated with fatigue in patients with IBD?	-Which potentially modifiable physical and psychosocial factors are associated with fatigue in patients with IBD?	-Which mechanisms of change are relevant, acceptable and useful when developing an intervention for the management of fatigue to patients with IBD?	-What is the feasibility of an intervention for the management of fatigue in patients with IBD? -What is the feasibility of a trial protocol for delivering a full pragmatic RCT of an intervention for the management of fatigue in patients with IBD? - What are the initial estimates of efficacy of an intervention for the management of fatigue in patients with IBD?
Methods	Systematic review	Quantitative cross-sectional study	Patient and public involvement activity	Pilot intervention testing with nested qualitative component
Output	PhD Paper 1	PhD Paper 2	PhD Paper 3	PhD Paper 4
Results	-Lack of psychosocial interventions for fatigue in IBD with long-term effects -Consistent significant associations between fatigue and disease activity, depression, anxiety and sleep difficulties -Lack of longitudinal studies exploring modifiable predictors of fatigue in IBD	-Significant associations between fatigue in IBD and emotional, cognitive and behavioural factors drawn from self-regulation theory - Significant associations between fatigue in IBD and emotional, cognitive and behavioural factors associated with fatigue in other long-term conditions	-Intervention content acceptable and relevant to patients with IBD-fatigue - Need for IBD-specific examples - High readability level scores - Plain formatting	- Completeness of outcome data measures, feasibility of delivery and acceptability of the intervention progression criteria were met - Recruitment and retention progression criteria were not fully met - HCPs found the intervention broadly applicable but identified time, finance and

				<p>training constraints in the implementation of the intervention</p> <ul style="list-style-type: none"> - There was a significant difference in change of fatigue impact scores between Group 1 and Group 2
Conclusions for the intervention	<ul style="list-style-type: none"> - Need for further exploration of cognitive and behavioural factors associated with fatigue in IBD which could be targeted in interventions 	<ul style="list-style-type: none"> -Applicability of an intervention manual for fatigue in MS to patients with fatigue in IBD 	<ul style="list-style-type: none"> - Keep MS intervention manual content and structure, adding examples relevant to IBD - Lower readability level scores - Make formatting more acceptable to patients 	<ul style="list-style-type: none"> - Progression to large-scale effectiveness RCT with changes to the protocol - Need to include strategies to improve recruitment, withdrawal and loss to follow-up rates - Consider online interventions to reduce barriers to implementation

Key: **HCP** – healthcare professional, **IBD** – inflammatory bowel disease, **MRC** – Medical Research Council, **MS** – multiple sclerosis, **RCT** – randomised controlled trial

2.6 Development Phase

The MRC guidelines advise substantial development work prior to the testing of the intervention. Indeed in the *development* phase of the MRC framework it is stated that before a full evaluation is conducted the intervention must be developed up to a point where a worthwhile effect can be expected. For the *development* phase the MRC advises to: identify the evidence-base, identify or develop theory and model processes and outcomes. Conducting a systematic review of what is already known about similar interventions and the methods that have been used to evaluate them is advised if there is no recent, high quality review available. Findings from this phase should then form the theoretical and empirical basis for developing an intervention.

2.6.1 Step 1: Identifying the evidence-base - Paper 1 (Chapter 3)

2.6.1.1 Existing systematic review evidence

In order to identify the evidence-base for the intervention, the development process was commenced by: defining and understanding the problem and its causes, and clarifying which causal or contextual factors related to the problem are malleable and have greatest scope for change. Indeed, it is important to look at previous evidence and use relevant information to inform new trials (Sutton et al., 2009) and a recent review found that 94% of the trials funded by the National Institute for Health Research Health Technology Assessment programme used a systematic review to inform a new trial design (Bhurke et al., 2015). As such, existing systematic reviews on the topic of fatigue and IBD were firstly sought to define the problem and its causes. Systematic reviews aim to collate all empirical evidence fitting a pre-specified eligibility criteria in order to answer a specific research question. They use systematic and explicit methods with the purpose of minimising bias, hence providing more reliable findings that can lead to conclusions being drawn and decisions made. Systematic reviews can be used to explore variations in practice, confirm the appropriateness of current practice or highlight a need for future research (Higgins and Green, 2011). Identifying systematic reviews on fatigue and IBD was therefore considered an effective way to define the problem of fatigue in patients with IBD, understand the causes of fatigue in patients with IBD and appraise current intervention practice for the management of fatigue in patients with IBD. Two published systematic reviews were found (Czuber-Dochan et al., 2013a, Van Langenberg and Gibson, 2010).

The first review by Van Langenberg and Gibson (2010) set out to examine the literature and determine the prevalence of fatigue in IBD patients. Ten studies were included in the review. Quantifying IBD-fatigue as a common problem that needs to be addressed, the review reported a prevalence of fatigue ranging from 28% to 41% in IBD in remission and up to 86% in moderate to severely active CD. All studies in the review were published between 2002 and 2009, showing

a recent rising interest in this symptom. The increase in publications also possibly suggested a growing recognition of the importance of its understanding and management for patients. Nonetheless, of the studies included in this first review, only one assessed fatigue in IBD patients as the primary outcome and in the rest the focus of fatigue was secondary to the main findings of the study. This indicated the need for the undertaking of more studies with fatigue as a primary outcome in order to have a greater understanding of the symptom. A significant positive relationship between fatigue and disease activity, and a significant negative relationship between fatigue and health related QoL were identified. These relationships highlight both the need to effectively manage disease activity in order to potentially improve fatigue and the need to effectively manage fatigue in order to potentially improve QoL in patients with IBD. Finally, the review discussed the central but incomplete association between inflammation and fatigue, and the need to look beyond inflammation to other factors in order to gain a full understanding of fatigue.

The subsequent review (Czuber-Dochan et al., 2013a) aimed to establish what is known about how people with IBD describe their experience of fatigue, how it is managed and what factors are associated with the presence and severity of IBD-fatigue. It included 28 studies. The review reported a similarly high prevalence of fatigue in new studies since the publication of the previous review. The steady rise in prevalence of IBD-fatigue confirmed the need for fatigue-management interventions to be developed. Fatigue assessment with 9 different non-IBD specific scales, highlighted the need to design studies utilising IBD-fatigue specific scales in the future. The review reported multiple physical, psychological and situational factors associated with IBD-fatigue. These associations strengthened the view of fatigue as a multifactorial phenomenon which should be targeted through multidimensional interventions. Lastly, the review summarised the results of three pharmacological and two non-pharmacological interventions for the management of fatigue. Including the same pharmacological studies included in 2010 which did not utilise fatigue as a primary outcome, the review did not provide further information on pharmacological management for fatigue. Likewise, the small samples and effect sizes, and short term effects of the non-pharmacological trials provided no definitive conclusions on which non-pharmacological interventions should be pursued.

2.6.1.2 The need for another review

The two existing systematic reviews were helpful in defining and quantifying the problem by recognising the prevalence of IBD-fatigue, its significant negative effect on QoL and the consequent need to develop effective interventions for its management. The reviews recognised fatigue as a multidimensional and multifactorial phenomenon with physical, psychological and situational causal underpinnings and the need to address these through the combination of different

therapeutic approaches. Additionally, the sparsity of interventions for IBD-fatigue management with significant and long-term effects and the need to design more interventions for fatigue specifically was a clear outcome of both reviews. Nonetheless, some questions remained unanswered that raised the need for another systematic review to be conducted. The existing reviews identified multiple causal factors for fatigue. However, they did not differentiate between associated factors which were amenable to interventional modification and those which were not. Additionally, taking into account the growth in the number of studies between the first review search on June 30th 2009 (Van Langenberg and Gibson, 2010) and the second review search on August 3rd 2012, a search for new studies published after then was deemed necessary. Indeed, the value of a systematic review is optimised when it is kept up to date and evidence is continually evolving as new research becomes available (Moher and Tsertsvadze, 2006).

A systematic review (Artom et al. 2016a; PhD Paper 1) aiming to systematically search and synthesise available evidence on potentially modifiable factors contributing to IBD-fatigue and what advances in the management of fatigue in individuals with IBD had been made was therefore undertaken. The review attempted to answer the following questions: i) What are the modifiable factors associated with presence and severity of IBD-fatigue? and ii) What are the modifiable factors, which have been previously targeted by interventions for the management of IBD-fatigue? A systematic search for new studies published since the search of the previous review (Czuber-Dochan et al., 2013a) in August 2012 [$n = 21$] and a reselection of papers [$n = 28$] included in the previous review according to the aims of the current review were conducted in April 2015. The search included quantitative observational designs [case control, cohort, or cross-sectional studies] and experimental studies (RCTs, quasi-experimental RCTs, non-RCTs, and pilot and feasibility studies). Following the MRC guidelines for the *development phase* of complex intervention development (Campbell et al., 2007), the present systematic review was therefore specifically designed to identify opportunities for intervention in fatigue research that could result in meaningful improvements in IBD-fatigue.

As the aim of the overall PhD project was to develop an intervention for the management of fatigue in IBD, the identification of opportunities for intervention in the existing literature was considered a necessary step in order progress to the next step of *identifying components of the intervention*. Structuring the review into modifiable and non-modifiable physical and psychosocial factors provided a practical means to identify factors not amenable to interventional modification and factors to be potentially included in interventions to improve IBD-fatigue. Furthermore, it was thought to aid in establishing potential components of the intervention according to its modality (pharmacological or non-pharmacological). The inclusion in the review of IBD-fatigue management interventions aided the identification of existing therapeutic

strategies for fatigue which could be drawn on when developing the intervention. Lastly, it facilitated the detection of factors which had not been previously explored by existing studies but could be included in the intervention. A justification of how part of the results of the systematic review informed the next steps of intervention development is presented in *Section 2.6.2. Identifying components of the intervention*, however full results of the systematic review are presented in Paper 1 (Chapter 3) of this PhD thesis.

2.6.2 Step 2a: Identifying components of the intervention - Paper 2 (Chapter 4)

2.6.2.1 Using the systematic review results to identify components of the intervention

The systematic review (Artom et al. 2016a) was utilised to feed into the Step 2a of the MRC framework and identifying components of the intervention. Indeed in order to obtain clear outcomes on the efficacy of the intervention, the rationale for inclusion of each component should be justified (Knowles et al., 2013a). Overall, the review showed an undue focus of existing IBD-fatigue research on the relationship between IBD-fatigue and non-modifiable situational and physical factors. The majority of studies concentrated on factors including female gender, unemployment, disease type and surgery. Although they were less explored, the review encouragingly identified a number of modifiable physical and psychosocial targets for the development of the intervention. Chiefly, consistent significant positive associations were found between IBD-fatigue and emotional factors such as depression, anxiety and behavioural factors such as sleep difficulties. People who displayed higher levels of depression, anxiety, stress and sleep difficulties reported significantly greater levels of fatigue. Furthermore, the strong evidence to support association between fatigue and disease activity substantiated pharmacological treatment of underlying disease activity as the first line strategy for the management for IBD-fatigue. In view of these findings, depression, anxiety, stress and sleep difficulties were selected as potential interventional targets of the intervention and were carried forward in the intervention development process. These were seen as particularly relevant in light of the systematic review evidence (Knowles et al., 2013a, McCombie et al., 2013, Gracie et al., 2017) to support the beneficial effects of psychological therapy on emotional and behavioural factors. Despite its importance, the medical management of disease activity was beyond the scope of this PhD project. The causal link between disease activity and fatigue was therefore taken into account in the next steps of the development process but did not form a part of the intervention. Patients who were experiencing an active flare of their IBD were not considered eligible for the intervention until treated.

Adding to the observational data on modifiable psychosocial factors associated with fatigue, initial findings from studies of IBD-fatigue specific non-pharmacological interventions included in the systematic review suggested promising effects for solution-focused therapy following pilot

testing (Vogelaar et al., 2011) and at 6 months' follow-up in a full-scale RCT (Vogelaar et al., 2014). After the 7-sessions solution-focused therapy course focusing on coping styles for fatigue, participants showed a greater reduction in fatigue and improvement of QoL compared to the care as usual group. Yet, the effect was not maintained at 9 months. Small reductions of fatigue were also shown with individualised exercise behavioural advice (McNelly et al., 2016). Participants who received an individual 15-minute consultation with a personal trainer providing advice to initiate in physical activity levels had lower fatigue levels measured by the Inflammatory Bowel Disease-Fatigue (IBD-F) scale (Czuber-Dochan et al., 2014a) compared to those receiving exercise placebo at end of treatment. However, there were no reductions in fatigue following exercise advice when using the Functional Assessment of Chronic Illness Therapy-Fatigue scale (Yellen et al., 1997), suggesting either limitations in the trial design and/or differential effects according to the specificity of the scale used. Together the mixed results from the above intervention studies (McNelly et al., 2016, Vogelaar et al., 2011, 2014) warranted further exploration of a psychosocial and/or behavioural intervention using more rigorous trial designs. The decision to develop a psychosocial intervention was therefore made.

2.6.3 Step 2b: Identifying appropriate theory - Paper 2 (Chapter 4)

2.6.3.1 Using the systematic review results to identify an appropriate theory for the intervention
Once the decision was made to develop a psychosocial intervention including the emotional (depression, anxiety, stress) and behavioural (sleep difficulties) factors identified in the review, Step 2b was undertaken to identify an appropriate theory. The incorporation of a theory is recommended by the MRC guidelines (Craig et al., 2008). Advantages of using theory in developing complex interventions have been previously described in *Section 2.3.1*. Nonetheless, aside from advising to undertake a systematic review of existing interventions the MRC framework does not provide practical procedures to assist researchers in identifying appropriate theory (Wight et al., 2015). The choice of the theory is left to the expertise of the investigators, their research questions and their disciplinary perspective (Hawe, 2015). In order to overcome this barrier in choosing an appropriate theory, specific attention was thus given to theories which have been utilised for the development of psychosocial interventions for fatigue in other long-term conditions. Drawing from interventions in other conditions can enhance the process of intervention development based on theory, without 'reinventing the wheel' (Lippke and Ziegelmann, 2008).

Quantitative (Jones et al., 2009, Kwakkenbos et al., 2015) and qualitative studies (Czuber-Dochan et al., 2013b, 2015), and systematic reviews (Artom et al. 2016a) have shown similarities between the perceived experience of fatigue between different disease groups. Although physiological triggers may be different, similar physical and psychosocial factors appear to be exacerbating and

maintaining fatigue across long-term conditions (Czuber-Dochan, 2015). Likewise cognitive and behavioural responses to symptoms of fatigue, such as avoidance of activity and focussing on symptoms (Deary et al., 2007, Spence and Moss-Morris, 2007), are common across medically unexplained symptoms (*i.e.* pain, headaches, constipation). Lastly, there is growing evidence for transdiagnostic approaches for treating mental health symptoms related to fatigue, such as depression and anxiety (Newby et al., 2015). Utilising a transdiagnostic approach to fatigue management, where interventions are based on the same underlying theories, may therefore be a viable option to address common processes in the perpetuation of fatigue while still addressing issues specific to the individual conditions. Once perpetuating factors of fatigue across conditions have been identified, the individual predisposing and precipitating aetiological factors underlying the specific condition can be addressed (Chalder and Willis, 2017).

2.6.3.2 Self-regulation theory (Leventhal et al., 1980)

Many of psychosocial interventions for fatigue conditions which included emotional and behavioural factors in other long-term conditions (Gielissen et al., 2006, Hewlett et al., 2011, van Kessel et al., 2008) are based on self-regulation theory (Leventhal et al., 1980). Self-regulation theory provides a framework for describing and understanding processes relative to the initiation and maintenance of behaviours for the self-management of illness threats (Leventhal et al., 2016). Self-regulation theory states that the way people think about their illness can have a significant impact on the way they behave in relation to their illness and its associated symptoms. Self-regulation theory proposes that patients develop illness perceptions in order to understand health threat. Illness perceptions can be subdivided into five core dimensions. Perceptions of i) the identity of the illness consisting of the label as well as the symptoms that are associated with the illness, ii) the causes of the illness, iii) the consequences of the illness, iv) the extent the illness can be controlled and v) the course of the illness and the duration of the symptoms (Leventhal et al., 2003). According to this theory, these illness perceptions then determine how people cope with their illness and therefore which emotions they experience and which cognitive and behavioural strategies they use to deal with their illness and associated symptoms. If people have more positive perceptions of their illness and their symptoms, they will cope better, experience more positive emotions and utilise more positive cognitive and behavioural strategies to deal with them. If people have more negative perceptions, they will not cope as well, they will experience more negative emotions and utilise more negative cognitive and behavioural strategies to deal with their illness (Hagger and Orbell, 2003).

2.6.3.3. Application of self-regulation theory in other long-term conditions

Drawing from an example of a long-term condition which is similar to IBD in its inflammatory and relapsing and remitting nature, a model was developed to explain and improve fatigue in multiple sclerosis (MS) utilising self-regulation theory (Van Kessel and Moss-Morris, 2006). In the model, symptoms of fatigue activate perceptions of fatigue and a representation of the individual's present condition is formed by integrating current fatigue symptoms and contextual information with these pre-existing beliefs. This representation guides the selection of coping behaviours (*e.g.* avoidance/resting, all-or-nothing behaviour). At the same time, the symptoms or cues trigger activation of emotional responses and awareness of these emotional responses prompts the selection and use of strategies for controlling these emotions. When the model was applied to an intervention for the management of fatigue, patients who undertook cognitive behavioural therapy (CBT) to modify fatigue-related negative cognitions and behaviours had significantly higher levels of fatigue reduction compared to patients doing relaxation therapy (van Kessel et al., 2008). Specifically, mediation analysis conducted after the trial (Knoop et al., 2012) confirmed that change in negative perceptions of fatigue mediated the change in fatigue as a result of the CBT. Thus, having more positive views about fatigue was closely related to the reduction of fatigue severity.

2.6.3.4 Application of self-regulation theory in IBD

Although self-regulation theory has never been applied for the understanding of IBD-fatigue specifically, an extensive evidence base exists to show that illness perceptions play a major role in the coping and adjustment of patients with IBD. Illness perceptions have been found to be associated with both general (Rochelle and Fidler, 2013) and disease-specific (Han et al., 2005) QoL. Patients who believe IBD would have serious consequences, those who do not perceive themselves to have control over their illness and those who think their illness will last for a longer time, display lower QoL scores (Rochelle and Fidler, 2013). Likewise, patients who perceive more symptoms to be part of their IBD have significantly worse IBD-related QoL (Han et al., 2005). Disability has also been found to have a relationship with illness perceptions, with illness perceptions accounting for a significant percentage of the explained variance in IBD disability in addition to demographic and clinical characteristics (Dorrian et al., 2009, van der Have et al., 2015). Furthermore, illness perceptions have shown to have a significant direct influence on depression, anxiety and family functioning (Knowles et al., 2011, 2013b). More negative illness perceptions are associated with the decreasing of activity, which in turn is related to lower levels of mental and physical health, and greater activity and work impairment (van Erp et al., 2017). Lastly, illness perceptions have been associated with non-adherence to anti-TNF therapy. Patients who perceived their IBD to have a shorter duration and perceived fewer of their symptoms to be a consequence of their IBD displayed lower adherence (van der Have et al., 2016). Based on

evidence to support its use in the understanding of management of fatigue in other long-term conditions (Gielissen et al., 2006, van Kessel et al., 2008, Hewlett et al., 2011) and its previous application in the understanding of other IBD-related outcomes, a decision was therefore made on the use of self-regulation theory (Leventhal et al., 1980) for the PhD intervention.

2.6.3.5 The need for a quantitative study

Although quantitative evidence showed a consistent association between fatigue, emotional (depression, anxiety and stress) and behavioural factors (sleep difficulties), no quantitative study previously explored the association between fatigue and cognitive factors in IBD. Key elements of self-regulation theory applied to fatigue have therefore not been tested in the IBD population. Prior to proceeding to Step 3 (modelling) and developing the intervention utilising self-regulation theory, it was therefore crucial to establish the relationship between fatigue and cognitive and behavioural factors as demonstrated by self-regulation theory through a quantitative study. Given that altering unhelpful illness perceptions and cognitions can improve clinical and psychosocial outcomes in long-term conditions (Broadbent et al., 2009, Seyyedrasooli et al., 2013, Yan et al., 2014), determining how cognitive-behavioural factors interrelated with those emotional, clinical and socio-demographic factors already known to predict fatigue in IBD, was considered the best way to test self-regulation theory and ultimately translate this research into an IBD-fatigue intervention.

The MRC framework states that in order to understand what changes are expected and how change is achieved because of the intervention, a theoretical understanding of the processes of change is needed. If the available evidence is insufficient, this can be done by supplementing it with new primary research. New primary research was therefore undertaken to determine which cognitions, emotions and behaviours should be targeted in the intervention. A quantitative cross-sectional study assessing factors associated with fatigue in patients with IBD was conducted (Artom et al. 2016b). Quantitative studies have been found to be important in designing trials to provide information on anticipated incidence in control groups, standard deviations when assessing continuous outcomes and choice of baseline characteristics for adjustment analysis (Djurisic et al., 2017). The overall aim of the study was to identify which physical and psychosocial factors were associated with fatigue in patients with IBD. The study included the physical and psychosocial variables associated with fatigue in the PhD systematic review (Artom et al. 2016a). Furthermore, the study included cognitive and behavioural factors which had been found to be associated with fatigue in other long-term conditions where interventions were available (Matcham et al., 2015, Chilcot et al., 2016, Skerrett and Moss-Morris, 2006), yet had never been previously explored in IBD. Specifically the study hypothesised that i) cognitive factors (illness perceptions and symptom beliefs) would be associated with IBD-fatigue

symptoms and IBD-specific QoL, ii) behavioural factors (resting behaviours, all-or-nothing behaviour, and daytime sleepiness) would be associated with IBD-fatigue symptoms and IBD-specific QoL and c) emotional factors (depression, anxiety, stress and distress) would be associated with IBD-fatigue symptoms and IBD-specific QoL. Full results of the quantitative cross-sectional study are presented in Paper 2 (Chapter 4) of this thesis.

2.6.4 Step 3: Modelling processes and outcomes – Paper 3 (Chapter 5)

2.6.4.1 Using the cross-sectional study to model processes and outcomes of the intervention

The cross-sectional study (Artom et al. 2016b; PhD Paper 2) was utilised to confirm that cognitive (illness perceptions and symptom beliefs), behavioural (resting behaviours, all-or-nothing behaviour, and daytime sleepiness) and emotional (depression, anxiety, stress and distress) factors associated with fatigue in other long-term conditions, were also associated with IBD-fatigue. One hundred and eighty-two participants were included in the study. In a hierarchical regression model, more negative fatigue perceptions were significantly associated with severity of fatigue. Likewise, more negative fatigue perceptions, all-or-nothing and avoidance behaviours were significantly associated with greater impact of fatigue on daily activities. Cognitive, behavioural and emotional factors explained an added 41% of the variance in impact of fatigue in addition to socio-demographic and clinical factors alone. As such, the overlap of cognitive and behavioural factors associated with fatigue between IBD and other long-term conditions suggested that self-regulation theory could effectively be utilised for the understanding of IBD-fatigue and for the development of an intervention for its management.

Based on the models using self-regulation theory in other long-term conditions (Skerrett and Moss-Morris, 2006, Deary et al., 2007) a cognitive behavioural model for breaking vicious cycles related to IBD-fatigue was developed (Figure 6). The logic model describes the inputs that the intervention involves, the processes that these initiate, and the mechanisms via which these are intended to realise positive outcomes. However, in attempt to develop a logic model it was found that the literature providing guidance on their development largely ignores how implementation and causal pathways may vary by context (Fletcher et al., 2016). Contextual factors are acknowledged in the model but the ways in which they interact with the rest of the factors remains unclear. A full description of intervention development is presented at the beginning of Chapter 5 of this thesis.

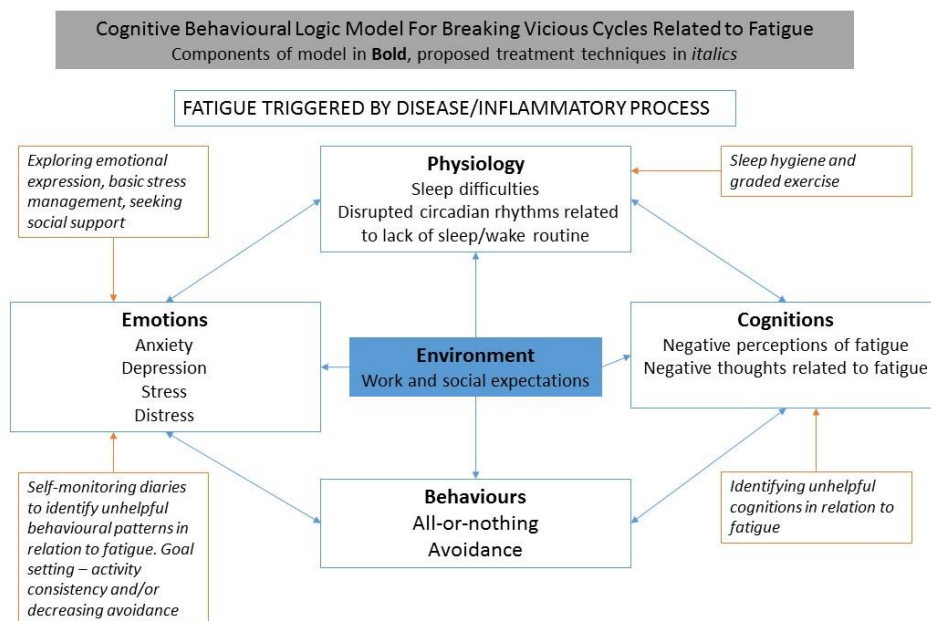


Figure 6: Proposed logic model for breaking vicious cycle of fatigue with intervention.

2.6.4.2 The need for a Patient and Public Involvement activity

In the MRC framework there is significant ambiguity about the optimal way to conduct the *modelling phase*. The proposed intervention has to be evidence-based and patient centred (*i.e.* in line with patient needs) (Vogelaar et al., 2011), yet there are no specific guidelines as to which theories should be utilised and/or how to collect patients' views. A Patient and Public Involvement activity involving patients with IBD, researchers and HCPs working with patients with IBD was therefore conducted in order to design the intervention manual. Full details of how the intervention manual was developed are provided at the beginning of Chapter 5.

2.7 Feasibility and piloting phase

2.7.1 Step 4 – Testing procedures

2.7.1.1 The need for a pilot study

As evaluations are often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment and retention and smaller than expected effect sizes, the MRC framework advises a piloting phase prior to the testing of a large-scale trial (Craig et al., 2008). Before rolling out a new intervention across a wide range of settings, intervention procedures should be evaluated for their acceptability, feasibility and efficacy. Depending on the results, further work may then be required to progressively refine the design of the intervention, before embarking on a full-scale evaluation. Beyond evaluative methodology, a pilot study can help the investigator examine the key uncertainties identified during the development of an intervention (Craig and Petticrew, 2013). A pilot study that clarifies aspects of the intervention's instructional

design can provide valuable data that the authors and other researchers in the field can use to test the proposed intervention components and mechanisms. Conducting a pilot study can reduce the proportion of failed trials and allow the progression of projects for which feasibility has been demonstrated and quantified (Leon et al., 2011). As such, the PhD intervention was tested in a pilot study prior to full-scale evaluation.

The protocol for the pilot study was published as PhD Paper 3 (Artom et al., 2017). It is recognised that this departs from traditional views of “publishable” work (Haji et al., 2014); however, well-constructed, articulate reports from pilot and feasibility phases are now viewed as worthwhile contributions by journal editors and other leaders in the field. Indeed, pilot data can be of practical utility for the PhD but also benefit the larger scientific community. Sharing pilot work experience, may provide solutions to problems that other investigators encounter as they pursue their respective research projects (Conn et al., 2010). Furthermore, publishing the protocol for the pilot study increases the transparency of the research process by providing a complete and detailed description of the intervention and how it was conducted. Making protocols publically available can allow a better appraisal of the quality of the study and ultimately reduce biased reporting (Chan et al., 2004).

2.7.1.2. The need for a randomised controlled trial

An RCT is recognised in the health and medical sectors as a gold standard for demonstrating the causal link between an intervention and an effect (Rychetnik et al., 2002). A clinical trial is indeed considered the method with the strongest internal validity, as well as the strongest scientific inference, minimising the risk of bias. Given that there is an inverse relation between internal and external validity, the superiority of clinical trial over any other design is based on the premise of the superiority of internal validity over external validity. The use of RCTs is not to represent ‘real situations’, but rather because experimental conditions are better able to generate definitive evidence. Neutralising external factors represents both the key strength of experimental design – scientific rigour being a matter of controlling elements – and its key limitation – as it does not aim to explain real-life effects (Tarquinio et al., 2015).

The limitation of experimental design is precisely that it minimises contextual factors that may, in fact, be essential to the success of the intervention (Tarquinio et al., 2015). This raises the issue of the transferability of results. Transferability has been defined as the extent to which the measured efficacy of an intervention could be achieved in another setting (Wang et al., 2006). Many factors – related to experimental conditions – could influence the transferability of results of health behaviour complex interventions, either directly (outcomes are not transferable because the terms and conditions for implementing the intervention are different) or indirectly (for the

same implementation modalities, different outcomes are obtained). These elements may include population characteristics, the environment in which the intervention takes place, the quality of the relationship between intervention participants, and the adaptations to the intervention made on the ground by the caregiver. Thus, challenges remain in measuring the effect of contextual elements to ensure that the studied intervention would produce the same results when implemented in another context (Cambon et al., 2012, Victora et al., 2004).

To overcome the limitations of RCTs, some authors have proposed adaptations to RCTs to bring this design closer to real-life conditions. These adaptations make it possible to test interventions in conditions closer to real life, *i.e.* to test the effectiveness of interventions and thereby maximise their transferability (Cambon et al., 2012). A second category of ‘adjustments’ to RCTs includes evaluation models using qualitative or mixed methods that aim to understand why a specific result was obtained and what could have contributed to it. Adapted models incorporate the analysis of process, components and mechanisms into evaluation models (Tarquinio et al., 2015). An adapted model, evaluating patients’ experience of the intervention using qualitative methods was chosen for the PhD intervention study.

2.7.1.3. The need for a nested qualitative study

Qualitative methods are viewed as particularly helpful at this early stage as they can respond flexibly to issues as they emerge (O’Cathain et al., 2015) and encourage an iterative approach to intervention development (O’Cathain et al., 2014). Qualitative methods can contribute in several ways to the design and refinement of an intervention by identifying intervention components in need of further refinement, barriers or facilitators to implementing an intervention and involving users in the development process (Lewin et al., 2009). A qualitative study can also inform changes to the intervention logic model, in advance a full-scale RCT (Figure 6, p. 58). There is the need to link data on outcomes with qualitative methods to tackle the questions of “how” and “why”. This shifts the focus from what works to which preconditions make certain outcomes more likely, for which people, and in which context. A simple binary of success or failure is not always helpful, especially if it precludes learning from multiple sources (Lamont et al., 2016). For these reasons, a nested qualitative study was included in the pilot study. Full details of the pilot study methods are presented in Paper 3 (Chapter 5). Full results at the intervention 3-months’ follow-up are presented in Paper 4 (Chapter 6) of this thesis.

2.8 Methodological conclusions

The overall aim of the study was to develop a complex intervention for the management of fatigue and test its feasibility and potential efficacy in patients with IBD. The methodological choices taken to achieve this aim were taken in attempt to avoid research waste and develop an

intervention that could be utilised by clinicians to improve IBD patients' care. Self-regulation theory (Leventhal et al., 1980) was utilised in the intervention development to identify which variables were to be changed by the PhD intervention in order to produce a significant change in fatigue and QoL. A logic model for the intervention was developed so as to improve the understanding of the causal assumptions of how the PhD intervention worked (Figure 6, p. 58). Reporting guidelines were followed in order to improve the accuracy and improve transparency of information. The SPIRIT checklist was utilised to guide the reporting of the intervention development in the published protocol for the intervention (Paper 3). The CONSORT statement was utilised to guide the report of the intervention results (Paper 4). Lastly, the MRC framework for the development of complex interventions (Craig et al., 2008) was utilised to guide each step of the intervention development process and identify the appropriate methods for their completion.

Chapter 3

3 Paper 1 - Targets for health interventions for inflammatory bowel disease-fatigue: a systematic review

This chapter presents an additional description and justification for the methods utilised for the systematic review (Artom et al., 2016a) published as Paper 1 of this PhD thesis. The published paper included Supplementary Table 1 (Appendix I) and Supplementary Table 2 (Appendix II). This includes a justification for the databases used and for the search terms and filters chosen for the systematic search. A statement of the contribution of the PhD student to this paper appears at the end of the paper on Page 81. Amendments to the published paper suggested by the PhD examiners following the oral examination are presented in Appendix XIX.



Original Article



Targets for Health Interventions for Inflammatory Bowel Disease-fatigue

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Abstract

Background and Aims: Fatigue is a complex, multifactorial, and multidimensional phenomenon. Recognition of modifiable correlates of fatigue can provide a further understanding of this phenomenon in patients with inflammatory bowel disease (IBD) and aid in the development of interventions tailored towards fatigue with potential for efficacy. Our aims were to systematically search and synthesise available evidence on potentially modifiable factors contributing to IBD-fatigue and what advances in the management of fatigue in individuals with IBD have been made.

Methods: The process of selection of citations was based on an earlier review by Czuber-Dochan *et al.* [2013] and was undertaken in two phases: i) searching for new studies published since August 2012, using seven electronic databases; ii) re-selection of papers included in previous review according to the aims of the current review.

Results: A total of 43 studies met the inclusion criteria. IBD-fatigue was consistently associated with disease activity, depression, anxiety, and sleep difficulties. However, most studies were cross-sectional; thus the direction of causation remains unknown. The relationship between biochemical factors, such as anaemia and inflammation, and fatigue was inconsistent. Solution-focused therapy, thiamine, and exercise showed promising effects on IBD-fatigue. Interventions continue to be sparse, with methodological limitations and only short-term effects reported.

Conclusions: The review identified a number of psychosocial and physical factors which could potentially be modified through targeted health interventions and improve fatigue in IBD. Research utilising prospective observational studies and randomized control trial (RCT) design is required to develop and test interventions to reduce fatigue, most likely within a biopsychosocial model of care.

Keywords: Fatigue; inflammatory bowel disease; management

1. Background

Fatigue is a complex, multifactorial, and multidimensional phenomenon, which limits individuals in their everyday lives.¹ Fatigue has been defined as a 'persistent overwhelming sense of tiredness, weakness, or exhaustion'² that can be mental, physical, or both.³ It is a common and predominant concern for individuals with inflammatory bowel disease (IBD)⁴ and can have a significant impact on patients' quality of life [QoL].^{5,6,7,8,9,10,11} Fatigue is experienced by

44–86% of IBD individuals with active disease and 22–41% of individuals in remission.¹² These prevalence rates have been corroborated by recent clinical outpatient¹³ and population-based studies¹⁴ where 52% and 59% of individuals with IBD reported fatigue, respectively.

Despite the high prevalence of IBD-fatigue, its causes are not well understood by either patients¹⁵ or healthcare professionals (HCPs),¹⁶ possibly affecting its management.^{12,17} The interventions so far are

often complex and insufficiently described,^{17,18} making it problematic to discern the active ingredients and how they are exerting their effect. In order to develop and test different methods to manage this symptom, it is important to view fatigue within a biopsychosocial model of care and consider how different physical and psychosocial factors interact with each other to explain IBD-fatigue and its severity. Multiple factors have been associated with IBD-fatigue, including: female gender, disease activity, anaemia, and depression.^{12,19} However, whereas situational and physical variables are not always open to change, psychosocial aspects underlying fatigue are potentially more amenable to modification. Recognition of modifiable correlates of fatigue can provide a further understanding of this phenomenon and aid in the development of interventions with potential for efficacy, which are specifically tailored towards fatigue.¹³

Previous reviews of the literature on IBD-fatigue focused on determining its prevalence and patterns¹⁹ and exploring how fatigue is experienced and managed.¹² IBD-fatigue has received growing attention in recent years,¹³ with an increase in the number of studies exploring predictors of fatigue which can be targeted by interventions. The purpose of this review is to systematically explore and to synthesise available evidence on potentially modifiable factors contributing to IBD-fatigue and what advances in the management of fatigue in individuals with IBD have been made. This will allow us to identify targets for health interventions to improve IBD-fatigue. Specifically, the questions addressed by the review are:

1. What modifiable factors are associated with presence and severity of IBD-fatigue?
2. What modifiable factors have been targeted by interventions for the management of IBD-fatigue?

2. Methods

The current review comprises a systematic search and a selective review. The process of selection of the retrieved citations [Figure 1] was undertaken in two phases: i) systematic search for new studies published since the search of the previous review by Czubier-Dochan and colleagues¹² in August 2012 [$n = 21$]; and ii) reselection of papers [$n = 28$] included in Czubier-Dochan and colleagues¹² according to the aims of the current review. Out of the 28 papers included in the previous review,¹² 22 met the revised criteria and were included in the review. Data specific to the review aims were extracted, analysed, and presented in a format addressing the questions set for the review [Table 1].

Seven databases were searched: MEDLINE [via OVID, 1946 to present], EMBASE [1980 to present], CINAHL [1981 to present], PsycINFO [2002 to present], Web of Science [1900 to present], the Cochrane Library, and the British Nursing Index. Both subject heading searching [MeSH] and free-text searching were used to maximise citation retrieval. The search combined the terms: fatigue [fatigue, tiredness, sleep, drowsiness, lethargy, exhaustion, lack or loss of energy, vitality, vigour] and IBD [IBD, inflammatory bowel disease, ulcerative colitis, and Crohn's disease]. For all databases, the final search was limited to articles in English language, original research, and adult subjects. Inclusion and exclusion criteria were defined utilising an amended version of the Population Intervention Comparison Outcome [PICO] approach for the analysis of observational and intervention studies.²⁰

The search included quantitative observational designs [case control, cohort, or cross-sectional studies] and experimental studies [randomised controlled trials [RCTs], quasi-experimental RCTs, non-RCTs, and pilot and feasibility studies]. Case studies were

excluded from the review. There were no restrictions on the basis of duration of follow-up. The population of interest was adults over 18 years of age with a diagnosis of IBD. Studies examining physical and psychosocial factors associated with IBD-fatigue were included in the review. Likewise, pharmacological and non-pharmacological intervention studies assessing changes in IBD-fatigue levels as the primary or secondary outcome were included [Table 2]. Manual searches were also conducted by scrutinising the reference lists of included papers.

Identified citations were transferred to 'EndNote7' and duplicates were removed [Figure 1]. One author [MA] screened all titles and excluded those that were obviously irrelevant. All abstracts were reviewed independently by two review authors [MA, JS]. Full copy of potentially relevant papers was retrieved and screened for eligibility. Letters [$n = 3$] and meeting abstracts [$n = 14$] were excluded if full-text manuscripts or author-provided data were not available. In three studies where multiple publications came from the same study, Graff *et al.*,^{14,21} Jelsness-Jørgen *et al.*,^{7,22,23,24} and Opheim *et al.*,^{24,26} data were retained for uniquely assessed variables.

3. Results

A total of 43 studies were included in the evidence synthesis: 27 cross-sectional studies, 7 longitudinal studies, 1 quantitative secondary data analysis, 7 RCTs, and 1 open-label pilot study. Studies were conducted in outpatient settings and with population-based cohorts. Heterogeneity of study design and different measurements of fatigue precluded formal meta-analysis of the data; therefore a narrative synthesis of studies was conducted. A limited number of studies reported findings separately for ulcerative colitis [UC] and Crohn's disease [CD], precluding the analysis of differential associations with fatigue between the two conditions.

3.1. Quality appraisal

The quality of included papers [$n = 43$] was assessed using the Critical Appraisal Skills Programme [CASP] assessment tools specific to the methodological design of each study.²⁷ The same criteria were used as in the previous review¹² and points were deducted if: specific objectives and pre-specified hypotheses were not stated; measurement tools were not validated; insufficient details were provided regarding the methodology or data analysis; evidence of selective reporting of the findings was present; or limitations were not addressed. The studies were classified as high quality [$n = 15$], medium quality [$n = 19$], and low quality [$n = 9$] [Table 1]. It was considered that all studies had a potential to contribute to knowledge development; therefore no studies were excluded on the basis of quality.

3.2. Factors associated with IBD-fatigue

Factors identified as associated with IBD-fatigue were classified as modifiable and non-modifiable. For clarity of presentation the modifiable factors associated with IBD-fatigue have been subdivided into physical [Table 3] and psychosocial factors [Table 4].

3.2.1. Physical factors

There was a consistent positive significant association between fatigue and IBD disease activity.^{5, 6, 9, 13, 14, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37} People with active disease had significantly higher levels of fatigue. Across studies, disease activity was assessed by one or more of the following measures with different cut-offs and combinations: i) faecal calprotectin; ii) standard clinical indexes [ie Clinical Activity

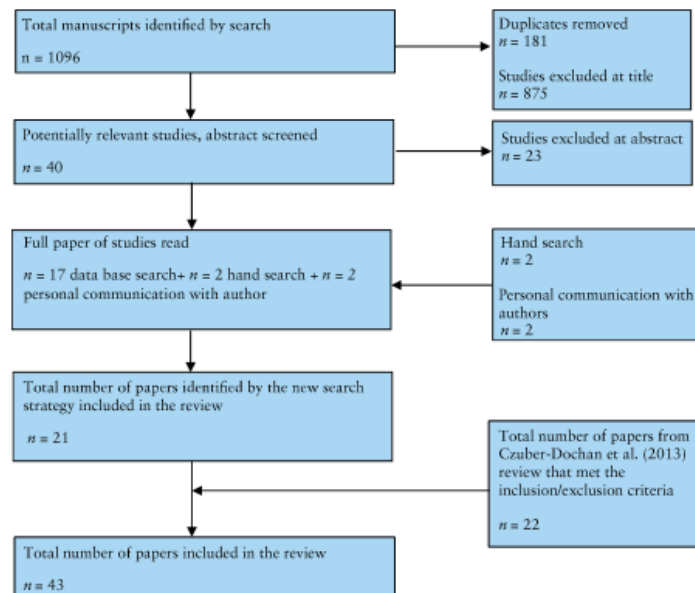


Figure 1. Flow-chart of citation retrieval and handling process.

Index, Mayo Score, and Simple Clinical Colitis Activity Index for UC; Crohn's Disease Activity Index, Harvey-Bradshaw Index, Short Crohn's Disease Activity Index for CD; Gastrointestinal Symptoms Activity Index for both; iii) endoscopic, radiological, and/or haematological investigations (Crohn's Disease Endoscopic Index Score, small bowel enteroclysis, inflammatory markers (haemoglobin, C-reactive protein [CRP], erythrocyte sedimentation rate, platelets, and albumin)) [Table 3]. Regardless of the known important role of inflammation in the pathogenesis of IBD,³⁸ only one study³² of those assessing these factors found a significant association between fatigue and increased platelet count and CRP.

Anaemia is suggested to be a primary causal factor of fatigue and its treatment is often chosen as the first line of fatigue management.³⁹ However, the relationship between fatigue and anaemia is not well understood. The definitions of anaemia varied widely across studies, making it difficult to discern what aspects to target in interventions.⁴⁰ The link between low haemoglobin and fatigue was supported by some studies^{7,22,28,37} but not others.^{9,14,21,35,41} Likewise, no significant correlations were found between iron deficiency and fatigue.^{34,35,41,42}

The use of corticosteroids to treat IBD inflammation was associated with greater levels of fatigue.^{5,13} Similarly, a positive correlation was found between the presence of fatigue and increased use of immunomodulators.^{5,13} Contrariwise, findings relating to the use of tumour necrosis alpha inhibitors (anti-TNF) and fatigue were more complex. Three small intervention studies reported that infliximab^{43,44} and adalimumab⁴⁵ significantly [$p < 0.0001$] improved IBD-fatigue. Two recent longitudinal observational studies found that anti-TNF use at baseline was linked to more severe fatigue⁴⁶ and the cessation of concurrent biologicals therapy was associated

with a reduction in fatigue.¹³ However, it is also possible for fatigue reduction to be an indicator of disease remission following treatment with anti-TNF therapy.

An inverse relationship was reported between fatigue and both physical functioning⁴⁶ and fitness.⁴⁷ Furthermore, in people with CD, objective muscle fatigue positively correlated with subjectively measured physical fatigue.⁴⁸ Research on the impact of nutritional factors on IBD-fatigue was limited. One study reported a weak but significant negative association between fatigue severity and albumin levels.³⁴ A small pilot RCT⁴⁹ found a significant deterioration in fatigue [$p = 0.02$] with omega-3 fish oil. Conversely, regular supplementation of vitamin B was associated with less physical fatigue in CD.¹⁹ People with IBD who smoked were significantly more likely to be fatigued compared with non-smokers.^{13,23}

3.2.2. Psychosocial factors

Both anxiety^{8,13,42,50} and depression^{6,8,11,13,29,30,41,42,46} were consistently associated with fatigue in IBD. Individuals who had higher scores of depression and/or anxiety had significantly higher levels of fatigue than those without. Lower psychological well-being was also independently associated with current fatigue³⁴ and with changes in fatigue severity over time.¹⁴ A number of studies highlighted a significant positive correlation between fatigue and daytime sleepiness^{42,50} and sleep problems in general.^{13,14,22} However, only one study looked at these aspects longitudinally.¹⁴ Thus, the direction of causation remains unknown. Some evidence supported the relationship between stress,^{21,24,30,51} distress,³⁴ and increased levels of fatigue. Likewise, people with fatigue had significantly worse valuations of their current health state⁶ and social functioning⁴⁶ compared with those without fatigue.

Table 1. Characteristics of included studies [*n* = 43].

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool[s]	Main findings	Study quality
Pharmacological and non-pharmacological intervention studies						
Costantini [2013] ¹⁸	To assess effectiveness of 1200 mg/day thiamine administered orally or parenterally	Open-label pilot study	12 [8 UG/4 CD]	CFS Scale	Ten/12 patients showed complete regression of fatigue [score 0]; 2/12 nearly complete regression of fatigue [score 3 & 5]. One patient treated with 1200 mg/day of thiamine showed a mild tachycardia that completely regressed by reducing the dose to 900 mg/day	Low
García-Vega & Fernández-Rodríguez [2004] ¹⁹	To assess effectiveness of stress management technique in reducing disease activity and improving psychosocial functioning in CD patients	RCT	45 CD	Semi-structured protocol designed by the authors	The self-directed stress management reported as significantly reducing tiredness post-treatment and at 6 and 12 months post-treatment Medical treatment plus psychological treatment seems to be more effective than medical treatment alone Placebo and actively treated patients reported symptom improvement Infliximab improved quality of life and decreased feelings of fatigue	Med
Lichtenstein [2002] ⁴³	Assess effect of infliximab on quality of life in patients with active CD	RCT, double-blinded	83 CD	IBDQ	At baseline patients' mean fatigue scores were 22.9 points Adalimumab reduced symptoms of fatigue and depression in patients with IBD	Low
Lofus [2008] ⁴⁴	Evaluate effects of adalimumab maintenance therapy on HRQoL in patients with moderate to severe CD	RCT double-blinded	854 CD	FACIT-F IBDQ SF-36	Baseline fatigue prevalence 86% Fatigue was significantly reduced by administration of a single dose of infliximab [patients with fistulae received one extra dose of infliximab 4 weeks after baseline]	Med
Minderhoud [2007] ⁴⁵	Measure effect of infliximab on fatigue, clinical disease activity, and depression scores	RCT, single blinded	14 CD	MFI IBDQ	Baseline fatigue prevalence 86% Fatigue was significantly reduced by administration of a single dose of infliximab [patients with fistulae received one extra dose of infliximab 4 weeks after baseline]	Low
McNelly [2015] ⁴⁶	To test effects of [i] individual advice to increase physical activity [PA] and/or [ii] supplementation with omega-3 on fatigue in IBD	RCT, 2 × 2 factorial study	74 IBD randomised, 60 started, 52 completed the intervention	FACIT-F IBD-F	There was a significant deterioration in FACIT-F score with the supplementation of omega-3 fish oil There was no significant difference on FACIT-F scores between those receiving and not receiving exercise advice. Fatigue was significantly reduced in the exercise groups, measured by IBD-F score SFT: fatigue level improved in 6/10 patients, in PST group 3 of patients improved fatigue scores, and in the CAU group 3/7 patients improved fatigue from baseline to 3 months' follow-up SFT had a positive effect on fatigue, better quality of life and fewer visits to the outpatient clinic	Med
Vogelaar [2011] ⁴⁸	To assess feasibility and effect of psychological interventions in the management of fatigue	RCT, pilot study	29 CD	CFS		Med

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool[s]	Main findings	Study quality
Vogelaar [2014] ¹⁷	To assess effectiveness of SFT RCT compared with CAU on fatigue and QoL in individuals with IBD fatigue	RCT	98 [40 UC/58 CD]	CIS-fatigue	At 3 and 6 months, scores were significantly better in the SFT group than in the CAU group. Significantly more individuals in the SFT group had a CIS-fatigue score below the cut-off point of 3.5 compared with individuals in the CAU group. The effect was no longer significant at 9 months	High
Longitudinal population-based and outpatient studies						
Banovic [2010] ¹⁴	Assess fatigue, disease activity, depression and anxiety, sleep disturbances, and subjective QoL	Longitudinal study	52 CD	MFI	Age and gender did not influence fatigue Longitudinal data Disease was inactive and there was no difference in fatigue score No significant difference between the two visits on the assessments of depression, anxiety, sleep disturbances, and subjective QoL	Low
Graff [2011] ¹¹	To evaluate psychological and biological factors in relation to fatigue	Population-based cohort study	318 CD	MFI	72% with active and 30% with inactive disease reached [clinical] threshold for fatigue Disease activity, poor sleep [but not hours of sleep], and perceived stress were associated with elevated fatigue Longitudinal data Fatigue was higher over time when disease was consistently active	Med
Graff [2013] ¹⁴	To assess fatigue longitudinally to determine the course of fatigue in IBD and the contributors to changes in fatigue	Population-based cohort study	312 [153 UC, 159 CD]	MFI at 12, 24 months follow-up	Poor sleep quality, distress, and lower psychological well-being, were significantly associated with changes in fatigue over time. Women and those who were younger were more likely to report higher fatigue Perceived stress was not statistically significant after the Bonferroni correction. CRP and Hb were not associated with fatigue over time	High
Kapleman <i>et al.</i> [2014] ⁸	To evaluate patient-reported outcomes in a cohort of patients with IBD and their associations between disease activity indices and IBD QoL	Longitudinal study Cross-sectional study	10 634 [3943 UC/6689 CD]; 2079 patients for the longitudinal analyses	4 items from each 6 PROMIS item banks [including fatigue]	Shorter disease duration, active disease, prednisone, and having a pouch were associated with worse fatigue Patients with fatigue had significantly lower levels of quality of life. Longitudinally, patients with worsening disease activity had worse fatigue and those with improving disease had improved fatigue scores. Older patients, men, and those with higher education levels reported better outcomes	Med

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool[s]	Main findings	Study quality
Rombert-Camps [2010] ¹²	To investigate the prevalence and severity of fatigue and the impact on HRQoL	Population-based registry prospective study	707 [304 CD/368 UC/35 indeterminate colitis]	MFI SF-36	MFI-20 dimensions general fatigue and physical fatigue were significantly worse in CD compared with UC and IBDU Disease activity and anemia were positively related with the level of fatigue In CD, patients using medication were significantly more tired than patients using no medication. Gender, age, length of follow-up, anemia, and the use of infliximab did not determine the level of fatigue. In UC, female gender was associated with higher fatigue scores, resulting in a worse score. Age, length of follow-up, and medication use were unrelated to fatigue	High
Van Langenberg [2014a] ¹³	To evaluate prevalence and severity of fatigue in CD [compared with UC and healthy controls] and to identify potentially modifiable factors associated with fatigue	Cohort study Cross-sectional study	311 [113 UC/181 CD/85 HC] at baseline 86 CD individuals at follow-up	FIS at baseline and follow-up for CD individuals, median time = 540	Current corticosteroid, immunomodulator and biologicals were significantly associated with higher fatigue scores. In CD, disease activity was associated with fatigue Multivariate logistic regression analyses Current active disease, sleep quality, depression, limited employment, smoking, and vitamin B group supplement use were associated with fatigue Small magnitudes of change were observed, mean changes in score = 0.9 for total fatigue	High
Vogelaar [2013] ¹⁶	To explore frequency of fatigue in two different hospitals, to explore the factors related to the risk for fatigue, and to investigate differences between disease phenotype in CD patients of a referral hospital and a general hospital	Longitudinal study	425 CD patients	CIS-fatigue	Patients in disease remission were less fatigued compared with patients with active disease Follow-up multivariate analyses Women were significantly more fatigued than men. A longer disease duration was associated with significantly less fatigue for men. More disease activity was associated with more fatigue. Patients using 5-ASA at baseline showed less fatigue, but when 5-ASA caused side effects, fatigue levels were higher at baseline Anti-TNF use at baseline associated with a higher fatigue level, maintaining anti-TNF through the follow-up year associated with a decreased fatigue level; this level was still significantly higher compared with that in non-anti-TNF users	Med

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool[s]	Main findings	Study quality
Cross-sectional studies						
Bäger [2012] ^{1a}	To investigate prevalence, characteristics and determinants of fatigue in IBD	Cross-sectional study	437 IBD	MFI	Fatigue scores were not significantly different between the UC and CD patients. Fatigue was significantly associated with disease activity and age [UC females]	High
Banovic [2012a] ^{1a}	To identify diagnostic variables of IBD-fatigue using the CART method	Cross-sectional study	118 [26 UC/92 CD]	MFI	Depressive mood, trait-anxiety, and daytime sleepiness were the most explanatory variables in patients with fatigue	Med
Banovic [2012b] ^{1a}	To determine relationships between personality and the perception of IBD-fatigue when disease is in remission	Cross-sectional study	135 [22 UC/59 CD]	MFI	No significant relationship between level of fatigue and duration of disease, number of relapses, number of flare-ups, number of quiescent periods, number of hospitalisations	Low
<p>Univariate analysis</p> <p>Significant relationship between level of fatigue and cumulative severity of intestinal resection, anxiety, daytime sleepiness, and self-directedness</p> <p>Multivariate analysis</p> <p>45% variance in fatigue [MFI] was explained by the value of PSHL daytime sleepiness, persistence, and self-directedness</p> <p>Fatigue was significantly positively associated with disease activity and depression</p>						
Björnsson [2004] ^{1b}	To evaluate well-being in patients with primary sclerosing cholangitis with focus on fatigue in comparison with IBD alone and matched with general population	Cross-sectional study	151 IBD from two hospitals, one in the UK and one in Sweden	FIS		Low
Bol [2010] ^{1c}	To study disease specificity of fatigue in multiple sclerosis and comparing its level with UC	Cross-sectional study	76 UC and 88 MS	MFI		Med
Castillo-Cejas et al. [2013] ^{1f}	To define applicability of three questionnaires and to define which had better application characteristics	Validation study	Validation Phase 99 [44 UC/55 CD]	DFHS	Validation phase	Med
	To determine the impact of fatigue on health perception in patients with IBD	Cross-sectional study	Questionnaire administration Phase 137 [70 CD/67 UC] + 69 HC	FSS	There was a significant correlation of QoL with the three fatigue questionnaires. There was a positive significant relationship between the degree of disease activity and the level of fatigue in the three questionnaires	
				MFI	There were no statistically significant differences between CD and UC	
					There was a significant relationship between clinical disease activity and fatigue. There was a significant inverse relationship between fatigue and QoL.	

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool(s)	Main findings	Study quality
Cohen [2014] ^b	To report the prevalence of fatigue in a cohort of newly diagnosed IBD individuals. To explore the relationship of fatigue with QoL, depression, and disability	Cross-sectional study	220 (95 UC/125 CD)	FACIT-F	No significant differences in fatigue prevalence between CD and UC CD individuals with active disease were significantly more likely to have fatigue than those with inactive disease [not significant in UC]. Significantly more women met fatigue criteria than men Fatigue was significantly associated with disease-specific [IBDQ] and general [SF-36, EQ-5D] quality of life Those with fatigue had significantly worse valuations of their current health state and were significantly more impaired in their daily activities. Working individuals with fatigue had significantly higher overall work impairment and absenteeism [CD only]. Depression was significantly greater with fatigue than without 49% of individuals with iron deficiency had high fatigue, 45% of individuals without iron deficiency had high fatigue [MH > 13]	Med
Goldenberg [2013] ^a	To investigate the relationship between iron deficiency and fatigue in IBD, in the absence of anaemia	Cross-sectional study	280 (128 UC/137 CD)	MFI	No mean differences in types of fatigue or fatigue outcomes between iron-deficient and iron-sufficient groups. Those with high fatigue had lower mean Hb than those without fatigue, but the difference was not significant Fatigue was significantly more likely to occur during active disease	High
Grimsstad [2015] ^a	To describe the prevalence and degree of fatigue in newly diagnosed and untreated IBD patients. Explore associations between fatigue, depression, and disease activity	Cross-sectional study	81 (60 UC/21 CD) + 67 HC	FSS and NVAS	Univariate analysis No significant associations between fatigue and disease activity, CRP or faecal calprotectin. FVAS scores were associated with CRP, ferritin, and depression. FSS scores were associated with calprotectin and depression Multivariate analysis HADS-D and age were significantly associated with fatigue. CRP, ferritin, calprotectin, and gender were not significantly associated with fatigue	High

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool(s)	Main findings	Study quality
Hauser [2005] ⁴⁶	To identify determinants of fatigue in IBD outpatients in remission or with slight disease activity	Secondary data analysis	37 UC with IPAA and 40 UC without ileal pouch-anal anastomosis	GSCI [fatigue subscale], SF-36	Fatigue had significant predictive value for Low reduced physical and social functioning Fatigue in UC patients was independent from objective disease measures in quiescent disease. Disease activity and depression were predictors of fatigue Neither age, gender, employment, nor education had statistically significant impact on fatigue IBD symptoms, Hb levels, and altered sleep patterns were significant predictors of chronic fatigue Fatigue was associated with increased IBD symptoms, smoking, and Hb values, reduced scores in general health and HQoL Increased levels of worrying were associated with increased fatigue levels and reduced QoL Presence of IBS correlated positively with total fatigue scores in UC and CD	Low
Jelsness-Jørgensen [2010] ¹²	Estimate level and frequency of fatigue among patients with mild to moderate IBD compared with healthy controls	Cross-sectional study	140 IBD patients [UC/CD 92/48] and 2287 healthy controls	FQ IBDQ		High
Jelsness-Jørgensen [2011] ⁷	To investigate influence of chronic fatigue on genetic and disease-specific HQoL	Cross-sectional study	140 IBD [UC/CD 92/48]	FQ SF-36 IBDQ		
Jelsness-Jørgensen [2012a] ¹⁴	To examine impact of fatigue on disease-related worries in IBD	Cross-sectional study	140 IBD [UC/CD 92/48]	FQ SF-36 IBDQ		
Jelsness-Jørgensen [2012b] ¹³	To investigate occurrence of fatigue among IBS-positive IBD individuals in remission	Cross-sectional study	140 [92 UC, 48 CD]	FQ		High
Kalaitzakis [2008] ⁸	Assess potential relation between fatigue and gastrointestinal symptoms in short bowel syndrome	Cross-sectional study	26 SBS [CD/UC 22/2], 41 IBD [CD/UC-13/28], 286 HC [SF-36]	FIS SF-36	Fatigue has a negative impact on QoL Fatigue was significantly associated with anti-TNF/immunomodulator therapy, depression, and anxiety. Fatigue was not associated with age, gender, or comorbidity 41% of IBD patients in remission suffered from fatigue	Low
Minderhoud [2003] ¹⁰	To assess the prevalence and severity of fatigue in IBD patients in remission	Cross-sectional study	80 IBD	MFI		Med
Norton [2015] ¹¹	To assess 3 fatigue assessment scales in IBD and to determine correlates of fatigue	Cross-sectional study	605 [164 UC, 301 CD]	IBD-F MFI MAF	Univariate analysis Females, CD patients [IBD-F, MFI], individuals with higher levels of anxiety and depression, had significantly higher levels of fatigue. IBDQ total scores were strongly associated with fatigue. Those working part-time and those not working had higher physical fatigue compared with individuals working full time [IBD-F, MFI, MAF] Multivariate analysis	High

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool[s]	Main findings	Study quality
Opheim [2014a] ¹³	To examine fatigue interference with daily living in IBD individuals and to explore relationships between severe fatigue interference and socio-demographic and clinical variables as well as CAM use	Cross-sectional study	428 [190 UC, 238 CD]	FSS-5	<p>IBD-F: 45% of variability of fatigue was predicted by female gender, depression, CD, and poorer QoL. MAF: age, depression, and IBDQ score were all independently associated with fatigue, 48% of fatigue was attributable to these factors. MFI: gender, depression, and IBDQ were all independently associated with fatigue, 42% of the variability in general fatigue could be attributed to these factors</p> <p>Female gender, CD diagnosis, and active disease were significantly associated with higher fatigue</p> <p>Univariate analysis</p> <p>Female gender, CAM use, active disease, the presence of at least one comorbid condition, were significantly associated with fatigue in UC. Disease activity, adverse drug reaction were significantly associated with fatigue in CD. Patients who were working or had a higher education level or income were less likely to report severe interference</p> <p>Multivariate analysis</p> <p>CAM use and disease activity remained factors independently associated with fatigue in UC. Current smoking and having an active disease remained independently associated with fatigue in CD</p> <p>Mean FSS-5 score was higher in CD patients compared with UC patients</p> <p>In UC, FSS-5 was negatively associated with lower scores on all 3 SOC sub dimensions. In CD, FSS-5 was negatively associated with manageability and meaningfulness</p> <p>Patients with IBD had more severe overall fatigue compared with non-IBD controls</p> <p>When considering IBD patients with mild to low active disease [$n = 11$], young IBD patients showed a non-significant trend toward higher fatigue</p>	Med Same study as [26]
Opheim [2014b] ²⁸	To explore associations between socio-demographic, disease-related, and personal variables and SOC	Cross-sectional study	428 [190 UC/238 CD]	FSS-5	<p>Mean FSS-5 score was higher in CD patients compared with UC patients</p> <p>In UC, FSS-5 was negatively associated with lower scores on all 3 SOC sub dimensions. In CD, FSS-5 was negatively associated with manageability and meaningfulness</p> <p>Patients with IBD had more severe overall fatigue compared with non-IBD controls</p> <p>When considering IBD patients with mild to low active disease [$n = 11$], young IBD patients showed a non-significant trend toward higher fatigue</p>	High Same study as [25]
Pellino et al. [2014] ¹⁵	To assess patient-reported fatigue in IBD patients and in controls	Cross-sectional study	16 IBD and 16 controls	FIS	<p>Patients with IBD had more severe overall fatigue compared with non-IBD controls</p> <p>When considering IBD patients with mild to low active disease [$n = 11$], young IBD patients showed a non-significant trend toward higher fatigue</p>	Med

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool(s)	Main findings	Study quality
Piche [2010] ¹³	To investigate the prevalence of IBS-like symptoms in CD patients in remission and impact of IBS-like symptoms on fatigue and QoL	Cross-sectional study	92 quiescent CD, 40 IBS and 20 healthy subjects	FIS	There were significant correlations between the severity of symptoms and QoL, the severity of fatigue, depression, and anxiety in both IBS and CD patients	Med
Romkens [2011] ¹⁸	To assess the prevalence and possible determinants of fatigue in IBD outpatients	Cross-sectional study	117 CD and 55 UC	FIS	64% reported fatigue regardless of clinical activity; 40% in clinical remission [HBI ≤ 5] reported fatigue None of the studied determinants of fatigue were significantly correlated with the presence of fatigue Patients with IBS and IBD were more fatigued than controls Patients with IBS were more fatigued than patients with IBD Psychological well-being, sleep disturbances, and employment status were independently associated with the severity of fatigue	Med
Simren [2008] ¹⁴	Evaluate factors of importance for fatigue in patients with chronic gastrointestinal diseases [IBS and IBD]	Cross-sectional study	223 IBD [UC/CD 133/90], 112 IBS	FIS	Patients with IBS were more fatigued than patients with IBD Psychological well-being, sleep disturbances, and employment status were independently associated with the severity of fatigue	Med
Tanaka [2005] ¹⁹	Elucidate factors influencing perception of difficulties of life and psychological well-being of patients with UC in remission	Cross-sectional study	72 UC	Questionnaire developed by the authors	Emotive coping, low social support, and high difficulties in life influence the scores for fatigue	Low
Tinsley [2011] ¹⁹	To validate the FACIT-F scale in IBD	Cross-sectional study	209 IBD	FACIT-F	Disease activity was significantly positively associated with fatigue levels Fatigue was not significantly associated to CRP. There were no significant differences in fatigue according to disease type	Med
Van Langenberg et al. [2014b] ¹⁶	To measure and compare self-reported fatigue with skeletal muscle fatigue in CD subjects and healthy controls, and to identify associated factors that may be amenable to change	Cross-sectional study	27 consecutive CD patients and 22 matched HC	FIS	The rate of muscle fatigue was significantly greater in the CD patients compared with controls. Maximal force production was not significantly different between the CD and control group There was a significant negative correlation between subjective physical fatigue and objectively measured rate of muscle fatigue. Those reporting greater fatigue via survey tended to demonstrate greater muscle fatigue as tested during exercise on the dynamometer	High

Table 1. Continued

First Author [Year of publication]	Aims of the study	Design	Sample	Fatigue tool(s)	Main findings	Study quality
Vogelaar <i>et al.</i> [2015] ¹⁷	To assess level of physical fitness and daily physical activity in IBD patients and whether fatigue is associated with impaired physical fitness and impaired physical activity	Cross-sectional study	10 IBD patients with fatigue and 10 without fatigue	CIS-fatigue	Fatigued patients showed a significantly lower intensity of daily physical activity (mobility) and an impaired physical fitness compared with non-fatigued patients Clinical characteristics such as surgery, disease activity, age at diagnosis, disease type, body composition, medication use and side effects to medication, were not significantly different between fatigued and non-fatigued patients	High
Yoo <i>et al.</i> [2014] ¹²	To investigate fatigue level and fatigue-related factors among Korean IBD patients	Cross-sectional study	128 [68 UC/60 CD] + HCs	FACT-F BFI	There was no difference in fatigue according to disease type In FACT-F and all sub-dimensions of BFI except walking ability, both UC and CD patients showed significantly increased fatigue symptoms compared with controls. In CD, ESR and disease activity were significantly correlated with global BFI in the unadjusted regression analysis; but after adjustment, none of the factors was statistically significant Anaemia was a significant determinant of both global BFI and FACT-F; ESR significantly correlated with FACT-F	Med

Anti-TNF, anti-tumour necrosis factor; BFI, Brief Fatigue Inventory; CAM, complementary and alternative therapies; CAU, care as usual; CD, Crohn's disease; CIS, Checklist Individual Strength – fatigue; CRP, C-reactive protein; DFS, Disease Fatigue Impact Scale; EQ-5D, Euro Quality of Life; ESR, Erythrocyte sedimentation rate; FACT-F, Functional Assessment of Chronic Illness Therapy-Fatigue scale; FIS, Fatigue Impact Scale; FQ, Fatigue Questionnaire; FSS, Fatigue Severity Scale; FSS-5, Five-Item Fatigue Severity Scale; IVAS, Fatigue Visual Analogue Scale; GSCL [Fatigue], Short Form Gleason Subjective Complaints List; Hb, haemoglobin; HRQoL, Health-related quality of life; IBD-E, Inflammatory Bowel Disease-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; IBDU, inflammatory bowel disease unclassified; HC, healthy controls; MAF, Multidimensional Assessment of Fatigue; MFI, Multidimensional Fatigue Inventory; MFI-S, Modified Fatigue Impact Scale; MS, multiple sclerosis; PFS, Piper Fatigue Scale; PSC, primary sclerosing cholangitis; PNH, Post Surgical Handicap Index; PST, problem solving therapy; QoL, quality of life; SBS, short bowel syndrome; SF-36, Health Survey Short Form-36; SOC, sense of coherence; SFT, solution-focused therapy; UC, ulcerative colitis; 5-ASA, 5-aminosalicylate.

Table 2. Adapted version of PICO table of inclusion and exclusion criteria.

	Inclusion	Exclusion
Population:	-Adults [≥ 18] -Individuals with IBD	-Children [< 18] -Individuals with other long-term conditions and no IBD -Individuals who have a diagnosis of CFS
Exposure/intervention:	-Individuals who have fatigue secondary to their IBD diagnosis -Any interventional approach	
Control/comparison:	-No comparison -Placebo -Treatment as usual/standard care -Waiting list -Alternative intervention	
Outcomes	-Studies examining the effect interventions to help alleviate IBD-fatigue as a primary or secondary outcome -Studies examining factors associated with IBD-fatigue as a primary or secondary outcome -Studies using a self-report fatigue scale -Studies using instruments developed by the authors to evaluate fatigue	
Study design:	-Quantitative studies -Observational studies -Experimental studies	-Qualitative studies -Reviews -Case studies -Editorials, letters or conference abstracts -Studies in non-English language

CFS, chronic fatigue syndrome; IBD, inflammatory bowel disease; PICO, Population Intervention Control Outcome.

Recent evidence also identified new psychosocial factors which appeared to be associated with improvements in IBD-fatigue. Individuals in remission who had a self-directed personality were less tired compared with those who did not have a self-directed personality.⁵⁹ Those who were more able to adapt their behaviour to fit the situation in accordance with their chosen goals had lower levels of fatigue compared with those who did not. Similarly, individuals with a higher sense of coherence experienced lower fatigue levels than individuals who had a lower sense of coherence.²⁶ For those who are more highly motivated to cope, understand the challenge, and have the resources to cope with it, fatigue may have less of an impact on their daily lives.

3.2.3 Non-modifiable factors associated with IBD-fatigue

In addition to the main review topics, a number of non-modifiable situational and physical factors have been found to contribute to the presence and/or severity of IBD-fatigue [Table 5]. However, many of these associations remain unclear, with conflicting data provided by different studies. Studies indicated that females reported significantly higher levels of fatigue than males.^{6,11,14,25,36,52} Individuals who were unemployed or had financial difficulties^{13,24,25,34,35} and those with lower education levels²⁵ also had increased fatigue. Some studies found no significant association between age and fatigue.^{6,13,22,25,28,30,34,46,52,54} Conversely, recent cross-sectional^{13,41,51} and longitudinal evidence¹⁴ showed younger age was associated with more severe fatigue. Although one study⁵¹ suggested that lower social support was related to decline in vigour in individuals with UC, findings were not supported by more recent evidence.^{13,23,34}

A negative association between length of time since diagnosis and fatigue was reported.^{9,30,36,51} Individuals with shorter disease duration had higher levels of fatigue compared with those who had lived longer with their IBD. While several studies found no differences in fatigue severity linked to disease type,^{5,6,14,21,22,35,37} others have found that people with CD experience higher levels of fatigue compared with UC.^{13,25,36,34} Number of relapses^{13,51} but not number

of IBD-related hospitalizations^{43,59} were positively associated with fatigue. Cumulative severity of intestinal resection was significantly associated with fatigue in individuals with IBD in remission.⁵⁹ For UC patients, having a pouch was associated with less fatigue compared with those in the highest quartile of disease activity, yet slightly more fatigue than patients in remission.⁹ Home parenteral nutrition was associated with worse fatigue.⁸ Some studies showed there was a significant association between fatigue and comorbidity.^{23,25,33} People with coexisting comorbidities, such as irritable bowel syndrome (IBS), had increased fatigue compared with those who did not have IBS or IBS-related symptoms.

3.3. Management of IBD-fatigue

Despite a growing number of studies assessing potentially modifiable factors associated with IBD-fatigue, few intervention studies have targeted these factors and the quality of these has been mostly low. Adding to the existing five interventions,^{16,45,44,41,56} since the publication of the review in 2013¹² only three interventions have been tested to address IBD-fatigue.^{17,49,57}

3.3.1. Pharmacological and physical management

Two of the pharmacological treatments addressed fatigue as the primary outcome.^{49,58} One intervention⁵⁸ was an open-label pilot study assessing the effects of thiamine on 12 individuals with IBD-fatigue. Ten participants showed complete regression of fatigue, and the remaining two showed a nearly complete regression of fatigue. However, the methodological limitations of the study, including the small sample, the lack of control group, and unsatisfactory statistical analyses, warrant caution in the interpretation of the above findings. The other study⁴⁹ was a randomised controlled 2 x 2 factorial pilot study comparing exercise advice [15-min consultation], omega-3 oil fish oil, a dietary consultation, and placebo. There were no significant positive effects of the interventions on fatigue levels, and omega-3 fish oil was associated with a significant deterioration in

Table 3. Potentially modifiable physical factors associated with IBD-fatigue [p-values in univariate analysis as reported in published papers].

First author [year of publication]	Disease activity	ESR	Platelets	CRP	Ferritin deficiency	Low Hb	Corticosteroids	Anti-TNF/immunomodulators	Exercise	Physical functioning/fitness	Muscle fatigue	Albumin	Omega-3 fish oil	Vitamin B	Smoking	Pain/Analgesics
Bager [2012]	+ve 0.05 [HbI > 4, SSCAI > 4]				N.S.	+ve 0.05 CD male										
Banovic [2010]	N.S. ^b [CDAI > 150]															
Banovic [2012a]	+ve 0.001 [GSRIS]				N.S.			N.S.								+ve 0.001
Bjornsson [2004]	+ve 0.01 [CAI]															
Boel [2010]	+ve 0.001 [HbI > 3, CAI > 6]															
Castillo [2013]	+ve 0.002 ^a [HbI > 5, SSCAI > 5]															
Cohen [2014]	+ve 0.001 [HbI > 5, SSCAI > 5]															
Goldenberg [2013]	+ve 0.001 [HbI > 5, Powell-Tuck > 5]				N.S.	N.S.										
Graff [2011]	+ve 0.001 [HbI > 5, Powell-Tuck > 5]				N.S.	N.S.										
Graff [2013]	+ve 0.001 [HbI > 5, Powell-Tuck > 5]				N.S.	N.S.										
Grimstad [2015]	N.S. [HbI > 5, MS > 2]				N.S.	N.S.										
Hauser [2005]	+ve 0.03 [CAI > 4]									-ve 0.05						
Jelness-Jorgensen [2010]			+ve 0.039	+ve 0.027		+ve 0.012										
Jelness-Jorgensen [2011]						+ve 0.05	N.S.									
Kalaitzakis [2008]																N.S.
Lichtenstein [2002]																
Lofrus [2008]																
Kappelman [2014]	+ve 0.001 [SCCAI > 150, SSCAI > 4]							+ve 0.001								
Minderhoud [2003]						N.S.										
Minderhoud [2007]								-ve 0.05								

Table 3. Continued

First author [year of publication]	Disease activity	ESR	Platelets	CRP	Ferritin deficiency	Low Hb	Corticosteroids	Anti-TNF/immuno modulators	Exercise	Physical function/ing/fitness	Muscle fatigue	Albumin	Omega-3 fish oil	Vitamin B	Smoking	Pain/Analgesics
Opheim [2014a]	+ve 0.001 [Hb] ≥ 4 , SCCAI > 3						N.S.	N.S.								+ve 0.09 ^a
Piche [2010]	+ve 0.0005 [CDAI > 150] ^d															
Romberg-Camps [2010]						+ve 0.05 ^b										
Simren [2008]	+ve 0.0001 ^c				N.S.											
Tinsley [2011]	+ve 0.001 [Hb] ≥ 5 , SCCAI ≥ 5			N.S.	N.S.	+ve 0.0001						+ve 0.01				
Van Langenberg [2014a] ^b	+ve 0.001 [Hb], SCCAI						+ve 0.003	+ve 0.03	-ve 0.001		+ve 0.05				-ve	+ve 0.05
Van Langenberg [2014b] ^c																
Vogelaar [2013]	+ve 0.001 [Hb] ≥ 5							+ve 0.002								
Vogelaar [2015]										+ve 0.037						
Yoo <i>et al.</i> [2014]	+ve 0.022 ^c [CDAI, $p = .016^b$ MS]				$p = .005^b$											

Anti-TNF, anti-tumour necrosis factor; CAI, Clinical Activity Index; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GSRS, Gastrointestinal Symptom Rating Scale; Hb, haemoglobin; HbA-Harvey Bradshaw Index; MS, Mayo Score; N.S., non-significant; SCCAI, Simple Clinical Colitis Activity Index; SCDAI, Short Crohn's Disease Activity Index.

^aOnly for CD individuals.

^bOnly for UC individuals.

^cDisease activity measured with calprotectin.

^dDisease activity measured with endoscopic, radiological, and/or haematological investigations (ie Crohn's Disease Endoscopic Index Score, small bowel enteroclysis, inflammatory markers [haemoglobin, CRP, ESR, platelets and albumin]).

^eDisease activity measured with haematological investigations (CRP, albumin, haemoglobin, and platelets).

+ve, positive association at $p < 0.05$; -ve, negative association $p < 0.05$.

Table 4. Potentially modifiable psychosocial factors associated with IBD-fatigue [p-values in univariate analysis as reported in published papers].

First author [year of publication]	Anxiety	Depression	Sleep problems	Daytime sleepiness	Worse self-valuation of current health	Distress	Stress	Social functioning	Psychological well-being	Sense of coherence	Self-directedness
Banovic [2010]	N.S.	N.S.									
Banovic [2012a]	Sig.	Sig.		Sig.							
Banovic [2012b]	+ve 0.005	+ve 0.001	N.S.	+ve 0.0009							
Bjornsson [2004]		+ve 0.01									
Bol [2010]											
Castillo-Cejas [2013]											
Cohen [2014]		+ve 0.001			+ve 0.001		+ve 0.01				
Graff [2011]											
Graff [2013]											
Grimstad [2015]		+ve 0.001	+ve 0.001			+ve 0.001			-ve 0.002		
Hausert [2005]		+ve 0.01									
Jelness-Jorgensen [2010]											
Jelness-Jorgensen [2011]			+ve 0.001					-ve 0.0001			
Jelness-Jorgensen [2012a]											
Kalaizakis [2008]	+ve 0.007	+ve 0.018					+ve 0.01				
Kappelman [2014]											
Norton [2015]	N.S.	+ve 0.001									
Ophelmin [2014b]											
Simren [2008]											
Tanaka [2005]											
Van Langenberg [2014a]	+ve 0.001	+ve 0.001	+ve 0.001				+ve 0.05		-ve 0.0001		

N.S., non-significant; Sig., significant but exact p-value not reported in text; +ve, positive association at $p > 0.05$; -ve, association $p < 0.05$.

Table 5. Non-modifiable factors associated with IBD-fatigue [p values in univariate analysis as reported in published papers].

First author and year of publication	Age	Gender – female	Education level	Unemployed, financial difficulties	Marital status / social support	Achieving full potential	Disease type: CD	Comorbidity	N of relapses/ flare-ups	N of hospitalisations	Length of time since diagnosis	Surgery	Ileostomy pouch	Home parenteral nutrition
Bager [2012]	+ ve 0.05													
Banerjee [2010]	UC female													
Banerjee [2012b]	N.S.	N.S.												
Bol [2010]	N.S.	N.S.												
Castillo [2013]														
Cohen [2014]														
Graff [2011]														
Graff [2013]	- ve 0.017	+ ve 0.001												
Grinstead [2015]	- ve 0.02	N.S.												
Hauser [2005]	N.S.	N.S.												
Jelsson-Jorgensen [2010]	N.S.	N.S.	N.S.	N.S.										
Jelsson-Jorgensen [2012a]														
Jelsson-Jorgensen [2012b]														
Kalirzikis [2008]	N.S.	N.S.												
Kappelman [2014]														
Norton [2015]	-ve 0.02	+ ve 0.03	N.S.	N.S.	N.S.									
Opheim [2014a]	N.S.	+ ve 0.004 ^b	- ve 0.04 ^a	+ ve 0.003 ^a										
Opheim [2014b]														
Pellino [2014]	- ve 0.06													
Piche [2010]	N.S.	+ ve 0.05 ^a												
Rombert-Camps [2010]														
Simren [2008]			N.S.	+ ve 0.0001	N.S.									
Tanaka [2005]														
Tinsley [2011]														
Van Langenberg [2014a] ^c	N.S.	N.S.	N.S.	+ ve 0.001										
Van Langenberg [2014b] ^c														
Vogelaar [2013]														
Yoo [2014]		+ ve 0.02												

BMI, body mass index; CD, Crohn's disease; N.S., non-significant.

^aOnly for CD individuals.^bOnly for UC individuals.^c+ ve, positive association at $p < 0.05$; - ve, negative association at $p < 0.05$.

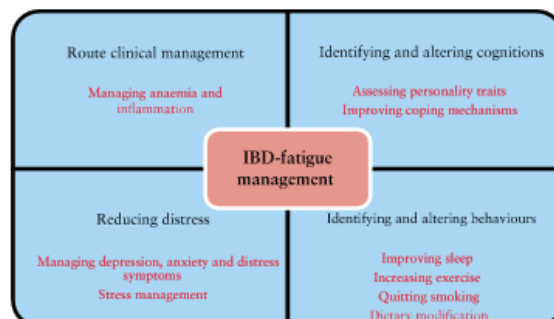


Figure 2. Proposed targets for health interventions for inflammatory bowel disease-fatigue.

fatigue scores [$p = 0.02$]. Conversely, the impact of fatigue was significantly reduced in the exercise group [$p = 0.03$].

Two RCT studies evaluated the effect of infliximab on fatigue in patients with active CD,^{43,44} and another⁴⁵ evaluated the effects of adalimumab maintenance therapy. Two of the studies^{44,45} measured fatigue as a secondary outcome utilising a fatigue-specific scale; in the other,⁴³ fatigue was assessed as a subscale of the Inflammatory Bowel Disease Questionnaire. Anti-TNFs were shown to have positive therapeutic effects, with a significant reduction in fatigue in the intervention groups. However, the high cost⁴⁹ and potential side effects⁴⁰ limit their application as first-line treatments for the management of IBD-fatigue. For a more detailed description of the interventions, see review by Czubier-Dochan *et al.* [2013]¹² or primary studies.^{43,44,45}

3.3.2. Psychosocial interventions

Three RCT studies evaluated non-pharmacological interventions for the management of IBD-fatigue. However, only two of the interventions^{17,18} were specifically developed to target fatigue in people with IBD. The first¹⁸ was a pilot RCT comparing problem-solving therapy [PST], solution-focused therapy [SFT], and care as usual [CAU]. The interventions were delivered by an expert psychotherapist. At 3 months' follow-up, individuals in the intervention arms showed a reduction in fatigue from baseline. The study had a small sample [$n = 29$] and a high attrition rate [21.6%], which limit the generalisability of the findings. Building upon the results from this pilot, the second RCT¹⁷ compared SFT and CAU in 98 patients with IBD. At 3 and 6 months, fatigue scores were significantly better in the SFT group than in the CAU group [$p < 0.001$]. The effect was no longer significant at 9 months [$p = 0.610$]. The third intervention¹⁶ compared professionally led stress management, self-directed stress management, and conventional medical treatment in 45 patients with CD. Fatigue was assessed as a secondary outcome. Following the intervention and at 6 and 12 months' follow-up, the self-directed stress management group showed a small, non-significant, reduction in fatigue [$p < 0.10$].

4. Discussion

Despite the wealth of studies assessing the relationship between IBD-fatigue and situational and physical factors, most of the factors are not amenable to interventional modification. In order to effectively treat those individuals with IBD-fatigue, it is henceforth important

to focus on reversible causes of fatigue, which can be targeted by health interventions within the knowledge and resource constraints of the health system.¹³ The aim of this review was thus to synthesise the knowledge on these potentially modifiable factors contributing to IBD-fatigue. The correlates of fatigue were grouped into physical and psychosocial factors.

The review highlighted the well-known link between disease activity and fatigue, with the majority of studies finding a positive association between active disease and IBD-fatigue. This is in line with findings in other relapsing and remitting conditions such as rheumatoid arthritis [RA]⁴¹ and multiple sclerosis [MS],²⁰ where patients display heightened levels of fatigue during relapses of illness. Similarly to other long-term conditions, including cancer⁴² and advanced kidney disease,⁴⁰ the relationship between fatigue and other biochemical factors was inconsistent. Some studies found a positive association between fatigue and inflammation,²² others did not.^{14,41} The correlation between fatigue and anaemia was supported by some^{7,34} studies but not all.^{10,31}

Although most studies focused on IBD-fatigue relative to physical factors, results from the present review showed a growing attention on the relationship between fatigue and psychosocial factors. Fatigue was consistently associated with depression, anxiety, and sleep difficulties in high quality studies, although the causative direction of the relationships is unclear. Furthermore, recent research highlighted the potential relevance of previously unexplored aspects, including personality⁵⁰ and cognitive factors.³⁶ Yet, apart from one study,¹⁴ these factors have been assessed cross-sectionally. Although limited in number, studies revealed an association between behavioural factors and fatigue, pointing at exercise⁶³ and smoking cessation^{13,25} as possible targets for interventions to reduce IBD-fatigue. This is consistent with other conditions, where the benefit of exercise on fatigue has been confirmed by trials.^{64,65}

Recent evidence from longitudinal observational research showing decreased fatigue associated with the discontinuation of biologicals and steroid therapy¹³ is of interest, especially in contrast with intervention data showing a possible positive therapeutic effect of infliximab^{43,44} and adalimumab⁴⁵ on fatigue. Indeed, in the RCT studies, the primary purpose of the intervention was not fatigue reduction and there was little or no apparent consideration of fatigue mechanisms in the design of the interventions. Viewing IBD-fatigue as a multifactorial and multidimensional phenomenon, a complex interplay of factors needs to be taken into account in the explanation and tackling of fatigue reduction. Disease activity

could be a confounder in the relationship. Moreover, corticosteroid therapy has been shown to frequently cause insomnia in patients with IBD,⁴⁶ ultimately leading to fatigue. Either way, these agents are associated with high remission and response rates and mucosal healing rates that are not achieved by other therapies,⁴⁷ making it difficult to make alterations to the treatment protocol to reduce fatigue. Conversely, findings from intervention studies utilising SFT^{17,18} are promising and show a renewed interest in treatment of fatigue as a clinical priority in the IBD population. Encouraging data from psychosocial interventions coupled with observational findings linking psychosocial factors to IBD-fatigue indicate this as a possible area of growth within the field.

4.1. Implications for research and practice

Lack of large-scale interventions based on a consistent model of fatigue and of long-term effects of existing interventions affirms the need for further interventional studies in the field, based on solid theoretical evidence.⁶⁸ Likewise, the methodological quality of observational studies varied, with only some of the studies applying multivariate analysis techniques to check for confounders. Different processes are likely to underlie fatigue.^{15,16} There is thus the need to develop integrated working models addressing multiple modifiable aspects and the interactions between them, similar to those in related conditions like MS⁶⁹ and RA.⁷⁰ For patients with active disease, according to large-scale longitudinal studies,^{5,13,14,36} the management of underlying inflammatory disease should be considered as the first line of treatment for IBD-fatigue. For those in remission and/or where fatigue cannot be explained by disease-related factors, there is an urgent need for studies with a prospective design so as to examine psychosocial factors as causal associations and potential mediators of IBD-fatigue.⁷¹ Indeed, longitudinally mapping the relationship between different factors associated with IBD-fatigue might aid in identifying those factors most appropriate for interventional change. Moreover, sub-group analysis according to non-modifiable demographic and disease-related factors should be considered in order to determine for which groups interventions would be more effective. Additionally, as disease activity was the most consistently associated factor with IBD-fatigue, there is the need to find a standardised way of measuring active disease in studies of IBD-fatigue. As more comprehensive research on modifiable aspects has been conducted in other illnesses, drawing from longitudinal studies^{70,71,72} and effective interventions developed in related conditions^{73,74} can provide better appreciation how these factors can be targeted in order to manage IBD-fatigue. For example, evidence from systematic reviews in MS and RA has shown that physical activity [ie aerobic, progressive resistance training, yoga] and psychosocial [ie cognitive behavioural therapy, mindfulness, energy conservation] interventions provide benefit in relation to self-reported fatigue.^{75,76} Additionally, it is important to develop interventions specifically focused on fatigue as they are more likely to show positive outcomes.⁴⁰ Evidence from studies which show that fatigue is similar between different disease groups, offers a real potential opportunity for the adoption of a systematic approach to the treatment of fatigue with the development of generic treatment approaches.⁷⁶

4.2. Strengths and limitations

This is the first systematic review which focuses on modifiable factors of IBD-fatigue. The review was conducted replicating a rigorous methodology previously utilised by Czuber-Dochan *et al.* [2013]. Abstract screening was carried out by two independent reviewers in order to minimise risk of bias. Despite the relative strengths of

this study, our findings should be considered in light of some limitations. Exclusion of studies in non-English language limits the generalisability of the findings cross-culturally. Some studies had small sample sizes, therefore the representativeness of these samples is difficult to assess. Moreover, the ways in which fatigue is measured vary and different studies utilise different thresholds when assessing fatigue. Similarly, studies used conflicting measures of disease activity, precluding generalisability across studies. Finally, as most of the included studies were cross-sectional, it is impossible to draw conclusions about causality.

4.3. Conclusion

The present review identified a number of modifiable factors which can be targeted by interventions to improve fatigue in patients with IBD within the existing health system. However, the complex interplay between these physical and psychosocial factors has yet to be unraveled, and it is unclear where the emphasis for interventions for fatigue should focus. Active disease and other biomedical conditions [ie anaemia] are related and treatments should potentially focus on addressing these factors first. However, not all fatigue will respond to these and there is a considerable percentage of patients without physiological underpinnings for fatigue, who also need intervention. It is likely that a biopsychosocial model may help the development of effective fatigue interventions.

Funding

None.

Conflict of Interest

WCD has received research funding from Crohn's & Colitis UK and served as a speaker for Crohn's & Colitis UK. CN has received funding and served as a speaker and an honorary adviser to the Board of Trustees, Crohn's & Colitis UK.

Author Contributions

MA, WCD, CN, JS designed the study. MA performed the literature search and review, and prepared the first draft. MA and JS selected the papers. All authors discussed the findings and prepared and approved the final version of the manuscript.

References

1. Beck A, Bager P, Jensen PE, Dahlerup JF. How fatigue is experienced and handled by female outpatients with inflammatory bowel disease. *Gastroenterol Res Pract* 2013;2013:153818.
2. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;56:157–70.
3. Arnett SV, Clark IA. Inflammatory fatigue and sickness behaviour. Lessons for the diagnosis and management of chronic fatigue syndrome. *J Affect Disord* 2012;141[2–3]:130–42.
4. Farrell D, Savage E. Symptom burden: A forgotten area of measurement in inflammatory bowel disease. *Int J Nurs Pract* 2012;18:497–500.
5. Castillo-Cejas MD, Robles V, Borrueal N, *et al.* Questionnaires for measuring fatigue and its impact on health perception in inflammatory bowel disease. *Rev Esp Enferm Dig* 2013;105:144–53.
6. Cohen BL, Zoega H, Shah SA, *et al.* Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014;39:811–22.
7. Jelsness-Jorgensen L, Bernklev T, Henriksen M, Torp R, Moum B. Chronic fatigue is associated with impaired health-related quality of life in inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;33:106–14.

8. Kalaitzakis E, Carlsson E, Josefsson A, Bosaeus I. Quality of life in short-bowel syndrome: impact of fatigue and gastrointestinal symptoms. *Scand J Gastroenterol* 2008;4:1057–65.
9. Kappelman MD, Long MD, Martin C, et al. Evaluation of the patient-reported outcomes measurement information system in a large cohort of patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014;12:1315–23.e2.
10. Minderhoud IM, Oldenburg B, van Dam PS, van Berge Henegouwen GP. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am J Gastroenterol* 2003;98:1088–93.
11. Norton C, Czubier-Dochan W, Bassett P, et al. Assessing fatigue in Inflammatory Bowel Disease: comparison and validation of three fatigue scales: IBD-F, MFI and MAF scales. *J Crohns Colitis* 2015;9:S209.
12. Czubier-Dochan W, Ream E, Norton C. Review article: description and management of fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;37:505–16.
13. Van Langenberg DR, Gibson PR. Factors associated with physical and cognitive fatigue in patients with Crohn's disease: A cross-sectional and longitudinal study. *Inflamm Bowel Dis* 2014;20:115–25.
14. Graff LA, Clara I, Walker JR, et al. Changes in Fatigue Over 2 Years Are Associated With Activity of Inflammatory Bowel Disease and Psychological Factors. *Clin Gastroenterol Hepatol* 2013;11:1140–6.
15. Czubier-Dochan W, Dibley L, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: An exploratory study. *J de Nurse* 2013;69:1987–99.
16. Czubier-Dochan W, Norton C, Bredin F, Darvell M, Nathan I, Terry H. Healthcare professionals' perceptions of fatigue experienced by people with IBD. *J Crohns Colitis* 2014;8:835–44.
17. Vogelaar L, van't Spijker A, Timman R, et al. Fatigue management in patients with IBD: a randomised controlled trial. *Gut* 2014;63:911–8.
18. Vogelaar L, van't Spijker A, Vogelaar T, et al. Solution focused therapy: A promising new tool in the management of fatigue in Crohn's disease patients: Psychological interventions for the management of fatigue in Crohn's disease. *J Crohns Colitis* 2011;5:585–91.
19. Van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2010;32:131–43.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
21. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis* 2011;17:1882–9.
22. Jelsness-Jorgensen LP, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis* 2010;17:1564–72.
23. Jelsness-Jorgensen LP, Bernklev T, Moum B. Fatigue and disease-related worries among inflammatory bowel disease patients in remission: is it a reflection of coexisting IBS-like symptoms? A short report. *J Psychosom Res* 2012;73:469–72.
24. Jelsness-Jorgensen L-P, Bernklev T, Henriksen M, Torp R, Moum B. Chronic fatigue is associated with increased disease-related worries and concerns in inflammatory bowel disease. *World J Gastroenterol* 2012;18:445.
25. Opheim R, Fagermoen MS, Bernklev T, Jelsness-Jorgensen L-P, Moum B. Fatigue interference with daily living among patients with inflammatory bowel disease. *Qual Life Res* 2014;23:709–19.
26. Opheim R, Fagermoen MS, Jelsness-Jorgensen LP, Bernklev T, Moum B. Sense of Coherence in Patients with Inflammatory Bowel Disease. *Gastroenterol Res Pract* 2014;2014:989038.
27. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007;36:666–76.
28. Bager P, Befrits R, Wikman O, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther* 2012;35:133–41.
29. Björnsson E, Simren M, Olsson R, Chapman R. Fatigue in patients with primary sclerosing cholangitis. *Scand J Gastroenterol* 2004;39:961–8.
30. Bol Y, Duits AA, Vertommen-Mertens CE, et al. The contribution of disease severity, depression and negative affectivity to fatigue in multiple sclerosis: a comparison with ulcerative colitis. *J Psychosom Res* 2010;69:43–9.
31. Goldenberg BA, Graff LA, Clara I, et al. Is iron deficiency in the absence of anemia associated with fatigue in inflammatory bowel disease? *Am J Gastroenterol* 2013;108:1392–7.
32. Hauser G, Tkalcic M, Pletikoscic S, Grabar N, Stimac D. Erythrocyte sedimentation rate-Possible role in determining the existence of the low grade inflammation in Irritable Bowel Syndrome patients. *Med Hypotheses* 2012;78:818–20.
33. Piche T, Ducrotte P, Sabate J, et al. Impact of functional bowel symptoms on quality of life and fatigue in quiescent Crohn disease and irritable bowel syndrome. *Neurogastroenterol Motil* 2010;22:e626–e174.
34. Simren M, Svedlund J, Posserud I, Björnsson E, Abrahamsson H. Predictors of subjective fatigue in chronic gastrointestinal disease. *Aliment Pharmacol Ther* 2008;28:638–47.
35. Tinsley A, Macklin E, Korzenik J, Sands B. Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;34:1328–36.
36. Vogelaar L, Van't Spijker A, Van Tilburg A, Kuipers E, Timman R, Van Der Woude C. Determinants of fatigue in Crohn's disease patients. *Eur J Gastroenterol Hepatol* 2013;25:246–51.
37. Yoo S, Jung YS, Park JH, et al. Fatigue severity and factors associated with high fatigue levels in Korean patients with inflammatory bowel disease. *Gut Liver* 2014;8:148–53.
38. Czubier-Dochan W, Dibley LB, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: an exploratory study. *J Adv Nurs* 2013;69:1987–99.
39. Krupp LB. Fatigue in multiple sclerosis: Definition, pathophysiology and treatment. *CNS Drugs* 2003;17:225–34.
40. Artom M, Moss-Morris R, Caskey F, Chilcot J. Fatigue in advanced kidney disease. *Kidney Int* 2014;86:497.
41. Grimstad T, Norheim KB, Isaksen K, et al. Fatigue in newly diagnosed inflammatory bowel disease. *J Crohns Colitis* 2015;9:725–30.
42. Banovic I, Gilbert D, Jebrane A, Cosnes J. Diagnostic profiles determined by the C.A.R.T. procedure: IBD patients and fatigue. *J Health Psychol* 2012;17:500–8.
43. Lichtenstein GR, Bala M, Han C, DeWoody K, Schaible T. Infliximab improves quality of life in patients with Crohn's disease. *Inflamm Bowel Dis* 2002;8:237–43.
44. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? *World J Gastroenterol* 2007;13:2089.
45. Loftus EV, Feagan BG, Colombel J-F, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008;103:1332–41.
46. Häuser W, Stallmach A, Kocalevent R-D, Rose M, Fliege H. Biopsychosocial predictors of fatigue in quiescent and mild ulcerative colitis-an explorative study. *Psychosoc Med* 2005;2:Doc. 07..
47. Vogelaar L, van den Berg-Emons R, Bussmann H, Rozenberg R, Timman R, van der Woude CJ. Physical fitness and physical activity in fatigued and non-fatigued inflammatory bowel disease patients. *Scand J Gastroenterol* 2015;50:1357–67.
48. Van Langenberg DR, Della Gatta P, Warmington SA, Kidgell DJ, Gibson PR, Russell AP. Objectively measured muscle fatigue in Crohn's disease: Correlation with self-reported fatigue and associated factors for clinical application. *J Crohns Colitis* 2014;8:137–46.
49. McNelly A, Nathan I, Monte M, Grimble G, Norton C, Bredin F, ... & Terry H. PTU-064 Inflammatory bowel disease and fatigue: the effect of physical activity and/or omega 3 supplementation. *Gut* 2015;64:A88.
50. Banovic I, Gilbert D, Jebrane A, Cosnes J. Personality and fatigue perception in a sample of IBD outpatients in remission: A preliminary study. *J Crohns Colitis* 2012;6:571–7.
51. Tanaka M, Kazuma K. Ulcerative colitis: factors affecting difficulties of life and psychological well being of patients in remission. *J Clin Nurs* 2005;14:65–73.

52. Romberg-Camps M, Bol Y, Dagnelie P, *et al.* Fatigue and health-related quality of life in inflammatory bowel disease: Results from a population-based study in the Netherlands: The IBD-South Limburg cohort. *Inflamm Bowel Dis* 2010;16:2137–47.
53. De Rooy EC, Toner BB, Maunier RG, *et al.* Concerns of patients with inflammatory bowel disease: results from a clinical population. *Am J Gastroenterol* 2001;96:1816–21.
54. Banovic I, Glibert D, Cosnes J. Crohn's disease and fatigue: constancy and co-variations of activity of the disease, depression, anxiety and subjective quality of life. *Psychol Health Med* 2010;15:394–405.
55. Pellino G, Sciaudone G, Caserta V, *et al.* Fatigue in inflammatory bowel diseases: Relationship with age and disease activity. *Int J Durg* 2014;12:S60–S3.
56. Garcia-Vega E, Fernandez-Rodriguez C. A stress management programme for Crohn's disease. *Behav Res Ther* 2004;42:367–83.
57. Costantini A, Pala MI. Thiamine and hashimoto's thyroiditis: A report of three cases. *J Altern Complement Med* 2014;20:208–11.
58. Costantini A, Pala MI. Thiamine and fatigue in inflammatory bowel diseases: An open-label pilot study. *J Altern Complement Med* 2013;19:704–8.
59. Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. *Mult Scler Int.* 2014;2014:798285.
60. Artom M, Moss-Morris R, Caskey F, Chilcot J. Fatigue in advanced kidney disease. *Kidney Int* 2014;86:497–505.
61. Nikolaus S, Bode C, Taal E, de Laar MA. Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res* 2013;65:1128–46.
62. Ahlberg K, Ekman T, Gaston-Johansson E, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet* 2003;362:640–50.
63. Nathan I, Norton C, Cramer-Dochan W, Forbes A. Exercise in Individuals With Inflammatory Bowel Disease. *Gastroenterol Nurs* 2013;36:437–42.
64. McCullagh R, Fitzgerald P, Murphy RPM, Cooke G. Long-term benefits of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: A pilot study. *Clin Rehabil* 2008;22:206–14.
65. Newman MA, Dawes H, van den Berg M, Wade DT, Burridge J, Izadi H. Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis: A pilot study. *Mult Scler* 2007;13:113–9.
66. Fardet L, Blanchon T, Perdoncini-Roux A, *et al.* [Internal medicine physicians' perception of frequency and impact of corticosteroid-induced adverse events]. *Rev Med Interne* 2009;30:113–8.
67. de Silva S, Devlin S, Panaccione R. Optimizing the safety of biologic therapy for IBD. *Nat Rev Gastroenterol Hepatol* 2010;7:93–101.
68. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;237:a1655.
69. Van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res* 2006;61:583–5.
70. Hewlett S, Chalder T, Choy E, *et al.* Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology* 2011;50:1004–6.
71. Cramer-Dochan W, Norton C, Bredin F, *et al.* Assessing fatigue in patients with inflammatory bowel disease. *Gastrointest Nurs* 2014;12:13–21.
72. Hewlett S, Ambler N, Almeida C, *et al.* Self-management of fatigue in rheumatoid arthritis: A randomised controlled trial of group cognitive-behavioural therapy. *Ann Rheum Dis* 2011;70:1060–7.
73. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme [MS Invigor8] for multiple sclerosis fatigue. *Behav Res Ther* 2012;50:415–21.
74. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med* 2008;70:205–13.
75. Cramp F, Hewlett S, Almeida C, *et al.* Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev* 2013;8:CD008322.
76. Jones D, Gray J, Newton J. Perceived fatigue is comparable between different disease groups. *QJM* 2009;102:617–24.
77. Bol Y, Smolders J, Duits A, Lange IM, Romberg-Camps M, Hupperts R. Fatigue and heat sensitivity in patients with multiple sclerosis. *Acta Neurol Scand* 2012;126:384–9.
78. Römken TE, van Vugt-van Pinxteren MW, Nagengast FM, van Oijen MG, de Jong DJ. High prevalence of fatigue in inflammatory bowel disease: A case control study. *J Crohns Colitis* 2011;5:332–7.

3.1 Justification for databases

The main characteristics of a systematic review are: clearly stated objectives, an explicit and reproducible methodology, pre-defined eligibility criteria for studies, a systematic search, an assessment of the validity of the findings of the included studies, and a systematic presentation of the characteristics and findings of the included studies (Higgins and Green, 2011). Conducting a thorough and well-documented search is one of the main distinctions between a systematic review and a literature review, and is a vital part of ensuring that the systematic review provides a rigorous and comprehensive summary of research evidence (Sackett et al., 1996). The ability to retrieve relevant material in a systematic review search depends on different factors including: expertise of the searcher (Havill et al., 2014), the quality of the database indexing (Papaioannou et al., 2010), the integrity of the software (Havill et al., 2014) and the content of the databases (Papaioannou et al., 2010). Searching the correct databases is hence important so as to ensure that as high a proportion as possible of relevant studies are identified (Suarez-Almazor et al., 2000). Likewise, those involved in reviewing the literature should be aware of how databases compare, so that gaps in coverage between databases can be identified and duplication of effort involved in searching multiple databases is kept to a minimum (McDonald et al., 1999). The majority of relevant papers appear in a limited number of databases and the choice of databases is topic-specific (Hartling et al., 2016). Furthermore, searches are often time-consuming and costly; therefore, there has been a growing interest in the trade-off between timeliness and exhaustiveness when preparing reviews (Peters et al., 2015).

MEDLINE was chosen as the first-choice database because it provides access to a broad range of biomedical literature coverage including nursing, and clinical and experimental medicine. It was thus considered an appropriate database for the search of articles related to IBD. EMBASE searches complement MEDLINE in several ways, by providing greater coverage of European and non-English-language publications and broader coverage of key topics such as pharmaceuticals and psychology, both of which were relevant in the present review (Wong et al., 2006). The overlap of EMBASE and MEDLINE is estimated to be 10% to 87%, depending on the topic (Royle et al., 2005). CINAHL was selected for its focus on nursing and allied health literature. This focus was considered helpful in capturing interventions for the management of fatigue delivered by nurses and allied health professionals (Brazier and Begley, 1996, Gargon et al., 2015). Similarly, the British Nursing Index was selected as it may be a source of choice for British nurses (Griffiths and Riddington, 2001). PsycINFO, which is a bibliographic psychological database, was used for the retrieval of articles related to psychological factors associated with IBD. Indeed, although it has some overlap with MEDLINE, its content area pertains to behavioural aspects of care and behavioural treatments for physical illness (Eady et al., 2008). The Cochrane Library was included as it provides enhanced access to reports of trials (Lefebvre

et al., 2008) and its use has been found to increase the search yield of conference proceedings and abstracts (Slobogean et al., 2009). Finally, Web of Science was utilised due to the multidisciplinary topic of the review (IBD and psychology) (Löhönen et al., 2010).

3.2 Justification for search terms and filters

The full search strategy for each database is presented in Appendix III. The search terms were identified replicating the rigorous methodology utilised by the previous review by Czuber-Dochan and colleagues (2013a). A major challenge of conducting a systematic review is to identify a tentative start set of search terms (Kitchenham, 2004). Using the same search terms as a previous related systematic review in the field can therefore aid in overcoming this problem. It has been suggested that replicating the searches conducted in a systematic review can strengthen the claims made by the original review, and build confidence about the validity of the systematic review methodology (Staples and Niazi, 2007). There is some evidence from a Cochrane review to support the use of checking reference lists for locating studies in systematic reviews (Horsley et al., 2011). The process was therefore incorporated in order to maximise citation retrieval. The choice of filters was more challenging, requiring the evaluation of pros and cons related to each filter. Systematic bias due to the selection of studies in a particular language is called a language bias (Egger et al., 2002). Bias may lead to an over or underestimation of an intervention's effectiveness, and ultimately, to inappropriate health policy decisions or patient care (Grégoire et al., 1995). It is consequently recognised that having relied exclusively on English-language studies may have missed important evidence on health interventions. However, the top international medical journals, by Journal Citation Reports impact factor, are English-language publications (Morrison et al., 2012). Furthermore, in a systematic review of use of language restrictions in systematic reviews and meta-analyses in conventional medicine (Morrison et al., 2012), no evidence was found of systematic bias for systematic reviews including only English-language publications.

Chapter 4

4 Paper 2 - The contribution of clinical and psychosocial factors to fatigue in 182 patients with inflammatory bowel disease: a cross - sectional study

This chapter presents an additional description and justification for the methods utilised for the cross-sectional study (Artom et al. 2016b) published as Paper 2 of this PhD thesis. This includes a justification for the cross-sectional study design and for the choice of the study questionnaires. The published paper included Supplementary Table 1 (Appendix IV), Supplementary Table 2 (Appendix V) and Supplementary Table 3 (Appendix VI). Eligible patients were provided with a Patient Information Sheet (Appendix VII) explaining the nature and aims of the study. Patients had the opportunity to take the questionnaires home and return them by post to fully consider their participation in the study and what participation in the study involved. A signed Patient Consent Form (Appendix VIII) was returned with the questionnaires by post.

The study was approved by the United Kingdom National Research Ethics Service – London Bridge Committee (15/LO/1081, Appendix IX). At the time of ethical approval, permission was granted also for clinical and questionnaire data collection at 12 and 24-months' follow-up points. Due to the limited time-frame of this PhD project, only the baseline results of the quantitative study were analysed and reported in this thesis. The main advantage of longitudinal studies is that participants are observed at more than one time point, thereby allowing trends in an outcome to be monitored over time (Sedgwick, 2014). However, the requirement for participants to commit to multiple data collection time points may have influenced their decision to participate or not and hence the sample that resulted (Payne and Hendrix, 2010, Albrecht and Taylor, 2013). A statement of the contribution of the PhD student to this paper appears at the end of the paper on Page 97.

Amendments to the published paper suggested by the PhD examiners following the oral examination are presented in Appendix XIX. Following the oral examination, analysis was conducted on the 12-month follow-up fatigue data. Findings of the additional analysis are presented in Appendix XX.

The contribution of clinical and psychosocial factors to fatigue in 182 patients with inflammatory bowel disease: a cross-sectional study

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Publication data

Submitted 30 June 2016
 First decision 19 July 2016
 Resubmitted 30 September 2016
 Accepted 29 October 2016

The Handling Editor for this article was Dr Ashwin Ananthakrishnan, and it was accepted for publication after full peer-review.

SUMMARY

Background

Fatigue is a frequently reported and predominant symptom experienced by patients with inflammatory bowel disease (IBD) and its impact has been associated with poorer quality of life (QoL). The complex interplay between disease-related variables and potentially modifiable psychosocial factors in IBD-fatigue has yet to be unravelled.

Aim

To evaluate the contribution of clinical, sociodemographic and psychosocial factors to the severity and impact of IBD-fatigue and QoL.

Method

In a cross-sectional study, 182 patients with IBD were recruited from three tertiary referral hospitals' out-patient clinics in London. Fatigue was assessed utilising the Inflammatory Bowel Disease-Fatigue Scale (IBD-F), the Multidimensional Fatigue Inventory (MFI); and QoL by the Inflammatory Bowel Disease Questionnaire (IBDQ). Patients completed self-report questionnaires evaluating emotional, cognitive and behavioural factors potentially correlated with fatigue. Sociodemographic data were collected. Disease-related and laboratory data were retrieved from patients' hospital electronic medical records.

Result

In hierarchical regression models, disease activity was the only clinical factor consistently associated with severity and impact of fatigue and QoL ($P = 0.01$). More negative fatigue perceptions were significantly associated with greater IBD-F1 scores ($P = 0.01$). When controlling for clinical factors (disease activity and anti-TNF therapy), negative perceptions of fatigue, and all-or-nothing and avoidance behaviours explained an additional 41% of the variance in fatigue impact (IBD-F2).

Conclusions

Apart from disease activity, emotional and behavioural factors and patients' negative fatigue perceptions may be key factors to be addressed. Further exploration of these factors in longitudinal and intervention studies may help to develop effective models of fatigue management.

Aliment Pharmacol Ther

INTRODUCTION

Symptoms of disabling and persistent fatigue are prevalent complaints within inflammatory, relapsing and remitting conditions.¹ Fatigue is one of the most frequently reported symptoms experienced by individuals with inflammatory bowel disease (IBD), with significantly higher fatigue severity scores being reported compared to healthy controls.² Although fatigue increases during periods of gastrointestinal inflammation, it also persists in some patients in whom disease is in clinical and endoscopic remission.³ Prevalence of fatigue ranges between 44% and 86% in active IBD and 22–41% in those with quiescent disease.⁴ Fatigue can be described as a mental and/or physical overwhelming sense of tiredness, weakness or exhaustion which is usually unrelieved by rest or sleep.⁵ The subjective nature of fatigue makes it difficult to report, assess and understand by both patients and healthcare professionals.^{6–8} Fatigue has been associated with poorer quality of life (QoL),⁹ and fatigued individuals with ulcerative colitis (UC) and Crohn's disease (CD) show significantly greater work impairment than those without fatigue.¹⁰

The aetiology of IBD-fatigue is still unclear.³ Disease activity,^{9, 11–13} anaemia^{14–16} and inflammation¹⁵ have been found to be predictive of fatigue, yet there is a considerable number of IBD patients with no apparent physiological underpinnings for their fatigue.¹⁷ The focus of previous research on the relationship between fatigue and these clinical variables has limited the exploration of how these and other potentially modifiable factors interact with each other to exert their effect.¹⁸

Fatigue has rarely been the primary outcome in intervention studies.^{19, 20} Effective management strategies remain sparse and with only short-term effects of interventions being reported.^{21–23} To develop interventions beneficial to patients,²⁴ it is important to shift from management of IBD aimed solely at treating inflammation and other clinical factors.²⁵ Working within a biopsychosocial model of care where clinical and psychosocial factors are identified and targeted alongside each other to restore patients' QoL may be more beneficial.^{26–28}

Initial data from studies exploring psychosocial interventions,^{20, 23, 29} coupled with observational findings linking IBD-fatigue to psychological distress^{13, 30, 31} and sleep problems,^{11, 13, 31, 32} highlight this as a promising area for intervention. However, most studies to date have been cross-sectional and very few interventional.⁴ Furthermore, unlike other long-term conditions,^{33–36} the

ways in which patients perceive, interpret and react to fatigue symptoms in IBD remain largely unexplored.³⁷

According to the Common Sense Model,³⁸ patients generate cognitive and emotional representations (illness perceptions) in response to their illness. Illness perceptions provide a framework for patients to make sense of their illness and in turn guide behavioural coping strategies, for example, resting or avoidance of activities, with potential impact on outcomes.^{39–41} Therefore, altering maladaptive cognitive representations and behavioural responses to symptoms can improve clinical and psychosocial outcomes.^{42, 43} Cognitive-behavioural therapy has been found to be effective in reducing fatigue levels in multiple sclerosis.^{44, 45} Changing negative representations of fatigue mediated the therapeutic effect of cognitive behavioural therapy in multiple sclerosis,⁴⁶ functional somatic syndromes⁴⁷ and irritable bowel syndrome.⁴⁸ The evaluation of the relationship between cognitive-behavioural variables and IBD-fatigue is thus of importance.

This study aimed to evaluate the contribution of clinical, sociodemographic and psychosocial factors to the severity and impact of fatigue and QoL in patients with IBD. Unravelling the complex interplay between clinical and modifiable psychosocial factors, can aid in developing potentially effective interventions for the management of IBD-fatigue, and ultimately improve patients' QoL. Given the findings from studies in other long-term conditions, this study investigated whether (i) emotional (depression, anxiety, distress and stress), (ii) cognitive (illness perceptions and symptom beliefs) and (iii) behavioural factors (avoidance and all-or-nothing behaviours, and daytime sleepiness) are associated with severity and impact of fatigue and QoL.

METHODS

Study design and population

The study followed a cross-sectional design assessing the association between fatigue and clinical, sociodemographic and psychosocial factors. Participants were recruited between September 2015 and March 2016 from the IBD services (out-patient clinics and biologic infusion units) at three tertiary referral hospitals in London. Patients with a documented diagnosis of IBD, aged 18 and over, with sufficient command of written and spoken English to complete self-report questionnaires were considered eligible for inclusion. Exclusion criteria were known cognitive impairment, currently on intravenous

iron therapy, pregnancy or childbirth within the last 6 months.

Sociodemographic and clinical data collection

Standard fixed choice questions were used to elicit details concerning age, gender, marital status, education, employment status and living arrangements. Smoking (yes/no/ex-smoker) and exercise status (< or >30 min of aerobic exercise per week) were recorded. Clinical information was obtained from the patients' hospital electronic medical records. Data on disease characteristics included: type of IBD diagnosis, length of time since diagnosis, number of IBD-related surgeries, current stoma, current IBD-related medication [aminosalicylates (5-ASAs), thiopurines, methotrexate, anti-tumour necrosis factor (anti-TNF), vedolizumab, antibiotics and steroids] and Disease Activity Index (DAI) scores [measured the Harvey-Bradshaw (HBI)⁴⁹ for CD or the Simple Clinical Colitis Activity Index (SCCAI)⁵⁰ for UC and the latest measurement of faecal calprotectin concentration]. HBI and SCCAI scores are intended to be calculated by the clinician at each out-patient clinic appointment and/or infusion clinic as part of patients' routine clinical care. Patients also completed a self-reported DAI, according to disease type, with the other study questionnaires. Previous studies have found a correlation between clinician-reported and self-reported scores for the both HBI⁵¹ and the SCCAI.⁵² Therefore, where a clinician-reported DAI score was not available (48%), the patient self-reported DAI was used. A score of ≥ 5 was taken as active disease in both conditions. No disease activity score was calculated for patients with a current stoma as the number of stools cannot be calculated ($n = 9$). Laboratory blood results were collected [haemoglobin, platelet count, ferritin, serum albumin, C-reactive protein (CRP), vitamin B12, folate and faecal calprotectin] if values for up to 3 months prior to or after the completion of the questionnaires were available.

Study questionnaires

Primary and secondary outcome variables. The primary outcome was fatigue, as measured by the IBD-Fatigue (IBD-F) Scale⁵³ and the Multidimensional Fatigue Inventory (MFI).⁵⁴ The IBD-F Scale was selected as it was specifically developed to measure IBD-specific fatigue. Higher scores indicate higher fatigue severity and greater impact of fatigue. Data assessing frequency and severity of fatigue from Section 1 (IBD-F1: five questions), and impact of fatigue on individuals' lives from Section 2 (IBD-F2: 30 questions) were included in the analysis.

Total scores for Section 1 and 2 are calculated separately. Questions in Section 2 are scored on a 0–4 Likert scale, with the possible total score range from 0 to 20. Questions in Section 1 are scored on a 0–4 Likert scale, with the possible total score range from 0 to 120. The MFI was chosen to be used in conjunction with the newly developed IBD-F scale, as it is the most frequently used scale to measure fatigue in IBD.⁹ It is a 20-item self-assessment instrument designed to measure the severity of multiple dimensions of fatigue (physical, mental and general fatigue, reduced activity and motivation). When a single score on fatigue severity is required results of the General fatigue subscale is recommended by the authors.^{54, 55} Indeed, the General fatigue subscale has been shown to have the highest correlation with general scales assessing fatigue severity in other long-term conditions.^{56, 57} Higher scores indicate higher fatigue. Due to the moderate sample size, continuous raw scores were utilised for both scales instead of categorical cut-offs (fatigued/nonfatigued).⁵⁸

The secondary outcome measure was health-related QoL as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ).⁵⁹ The IBDQ is a disease-specific measure of overall physical, mental and social well-being in patients with CD and UC. The scale has 32 items scored on a 7-point Likert scale, higher scores signify better QoL.

Predictors of the outcome variables. Based on findings in other conditions a decision was made to explore a number of emotional (anxiety and depression, stress and distress), cognitive (illness perceptions and symptom beliefs) and behavioural factors (avoidance and all-or-nothing behaviours, and daytime sleepiness) as potential predictors of the outcome variables.

The Hospital Anxiety and Depression Scale (HADS),⁶⁰ Cohen Perceived Stress Scale (PSS)⁶¹ and the Inflammatory Bowel Disease-Distress Scale (IBD-DS)⁶² were used to assess potential emotional factors associated with the outcome variables. The HADS was selected for this study as it was originally developed for physically ill patients and no items about somatic symptoms are included.⁶³ It is a widely used self-report instrument for assessing depression and anxiety in patients with medical illnesses⁶⁴ and it includes two subscales, anxiety and depression, each consisting of seven items (each scored 0–3). The two subscales are scored separately and higher scores indicate higher anxiety and depression respectively (maximum score for each = 21).

The PSS was developed to examine the role of stress in disease. It measures self-perceived stressful situations

and stress reactions on a cognitive and emotional level. The questionnaire contains 14 items, each is scored from 0 to 4; with a possible global score ranging from 0 to 56.

The IBD-DS is a newly developed scale designed to identify and measure disease-related distress in IBD in the last 3 months.⁶⁵ The scale consists of a number of questions which are scored on a 6-point Likert scale, ranging from 'Not distressing' to 'Highly distressing', with higher scores indicating higher distress.

Cognitive factors were assessed using The Brief Illness Perceptions Questionnaire (BIPQ)⁶⁶ and the cognitive subscales of the Cognitive Behavioural Response to Symptoms Questionnaire (CBSQ).³³ The study utilised a modified version of the BIPQ consisting of eight items: five assess cognitive illness representations (consequences, timeline, personal control, treatment control and identity); two emotional representations (concern and emotions) and one item assesses illness comprehensibility. The open-ended response item assessing the causal representation of fatigue was excluded from the questionnaire. In line with recommendations from the authors of the scale,⁶⁷ to make the questionnaire more relevant to the IBD patient group, the word 'illness' was replaced with 'fatigue'. This has been done in other studies^{68–70} assessing clinical and psychosocial outcomes in patients with long-term conditions to make the questions more specific to their topic of research. Each item is rated on a 0–10 scale. Given the known limitations of assessing content validity with single item measures⁷¹ and the increased risk of type 1 errors when using multiple testing,⁷² a total sum Fatigue perception score (ranging 0–80) was calculated as opposed to calculating scores for the individual subscales. Higher sum scores indicated more negative, unhelpful representations of IBD-fatigue. The CBSQ measures patients' cognitive and behavioural responses to their symptoms (of fatigue). It contains 40 items measured on a 5-point Likert scale. Items are added to form five cognitive subscales (fear avoidance, embarrassment avoidance, damage beliefs, symptom focus and catastrophising about symptoms). Higher scores indicate more negative cognitive responses to fatigue symptoms.

Behavioural factors associated with fatigue and QoL were assessed with the behavioural subscales of the CBSQ (resting and avoidance of activity and all-or-nothing behaviour) and the Epworth Sleepiness Scale (ESS).⁷³ The ESS measures a subject's level of daytime sleepiness by asking subjects to rate their chance of falling asleep on a scale of 0–3 in eight soporific situations, higher scores indicate higher propensity of falling asleep during

the day (maximum score = 24). The scale provides an assessment of interference of sleepiness during the day.⁷⁴

Ethical considerations

The study was approved by the United Kingdom National Research Ethics Service – London Bridge Committee (15/LO/1081). Eligible patients were provided with a Patient Information Sheet explaining the nature and aims of the study. Patients had the opportunity to take the questionnaires home and return them by post to fully consider their participation in the study and what participation in the study involved. Signed informed consent was returned with the questionnaires by post. All participants were allocated a study number to protect their anonymity.

Statistical methods

Statistical analyses were performed using SPSS version 22 (Armonk, NY: IBM Corp.). Missing data analyses were performed to assess extent and patterns of missing data for the study. Count variables were created for each of the scales (cut-off of 80%), mean and total scores were computed for each of the items. Overall 6% of all values were missing, 92% of the 182 patients had at least one missing value in their responses and 72% of the variables had at least one missing value. Multiple imputations were selected as a method of handling missing data (five imputations), chosen because of its flexibility and generality, its effectiveness with moderate sample sizes⁷⁵ and its previous application in medical studies.⁷⁶ Data were not imputed for faecal calprotectin (66.5%), folate (52.2%), B12 (41.8%) and ferritin (39.6%) due to the high number of missing values for these variables and a complete case analysis was completed separately. Initial analysis was conducted according to diagnosis [UC, CD, Inflammatory Bowel Disease-Unclassified (IBD-U)]. However, as no significant differences were found between the groups, the data were analysed as a single group. Utilising G power 3.1.9.2 *post hoc* analysis,⁷⁷ it was estimated that with a sample size of 182 respondents and an alpha level $P = 0.01$ the statistical tests would be sufficiently powered to detect a moderate effect size.⁷⁸

Unadjusted associated correlations and differences between independent variables and fatigue levels (as measured by the IBD-F and MFI) and QoL (IBD-Q) were calculated using Pearson product-moment correlation coefficient for continuous variables, and independent samples *t*-tests and one-way between subjects ANOVAS for categorical variables. Factors associated with the outcomes in univariate analyses ($P < 0.10$) were then

included in multivariate regression analyses to identify independent predictors of fatigue and QoL. All regression models were fitted after testing assumptions were met for the variables involved.^{79, 80} A hierarchical regression model for the IBD-F1 was run in which fatigue was regressed upon sociodemographic and clinical factors in block 1 (education up to 16, education up to 18, retired, not working/housekeeping, female gender, single/single parent, divorced/widowed, disease activity, exercise <30 min per week, current smoking, ex-smoker and current thiopurines). Variables were entered in a final regression models using a two-block variable entry method hierarchical method.⁸¹ Block 1 was adjusted for sociodemographic and clinical predictors of the outcome variable (fatigue and QoL); in block 2, psychosocial variables were added (i.e. adjusted for block 1, sociodemographic and demographic variables). To control for multiple testing and control the probability of committing type I errors in families of comparisons under simultaneous consideration,⁸² the threshold for statistical significance in multivariable analysis was set at $P < 0.01$.

RESULTS

Total of $n = 414$ patients were approached for inclusion in the study. Of these 182 patients provided informed consent and returned the completed questionnaires via post (44% response rate). The sociodemographic and clinical data of participants are presented in Table 1. Data for those who declined consent could not be retrieved. Of those who completed the questionnaires ($n = 182$), 57% were female, 69% worked full time and their median age was 37.0 years (range 20–83 years). The majority (64%) of participants had CD, with a median of 12 years since diagnosis of IBD. Of the 88% of patients taking medication, 38% were on biologic medication (anti-TNFs or vedolizumab), and 4.9% ($n = 9$) patients had a stoma. Of those without a stoma $n = 45$ (26%) had active disease and $n = 128$ (74%) were in remission according to the DAI scores. Where data were available ($n = 174$), following the European Crohn's and Colitis Organisation guidelines for the management of anaemia in IBD⁸³ (<12 g/dL for adult women and <13 g/dL for adult men), 17% of participants were anaemic.

Univariate analysis

The results of univariate analyses are shown in Tables S1–S3. Pearson product-moment correlations were calculated to assess univariate associations between sociodemographic, clinical and psychosocial factors and fatigue (IBD-F1, IBD-F2, MFI) and QoL (Table S1). Disease

activity was significantly associated with fatigue and QoL across all scales. In addition, faecal calprotectin ($r = 0.47$, $P < 0.001$) and platelets ($r = -0.15$, $P = 0.03$) were significantly associated with QoL. No other sociodemographic or clinical variables were significantly related to fatigue or QoL. Emotional, cognitive and behavioural variables had positive significant correlation with both severity (IBD-F1 and MFI) and impact of fatigue (IBD-F2) and QoL, showing moderate to large effect sizes.

Independent samples t -tests were computed to assess the differences in fatigue and QoL scores between dichotomous sociodemographic and clinical variables (Table S2, identification of variables that met the $P < 0.10$ for entry into the multivariable model). On average, females reported significantly higher fatigue severity ($M = 10.07$, $SEM = 0.44$) and fatigue impact levels ($M = 35.64$, $SEM = 2.67$) than males ($M = 7.17$, $SEM = 0.53$; $M = 24.36$, $SEM = 2.91$). Individuals who did less than 30 min of exercise per week or had a stoma also reported higher levels of fatigue on all measures (IBD-F1, IBD-F2, MFI) and lower QoL. Those taking anti-TNF therapy (IBD-F2, MFI), methotrexate (MFI) or steroids (IBD-F2) had a significantly higher fatigue scores. Individuals on steroids or methotrexate had significantly reduced QoL compared to those not on these medications. Conversely, individuals taking thiopurines (IBD-F1) and 5-ASAs (IBD-F2) had significantly lower fatigue scores compared to those who did not. Patients taking thiopurines had better QoL scores ($M = 101.57$, $SEM = 1.43$) compared to those not on thiopurines ($M = 96.54$, $SEM = 1.55$). No significant differences in fatigue and QoL scores were found in respect to antibiotics, vedolizumab and past occurrence of surgery.

One-way between groups ANOVAs were computed to assess differences between fatigue and QoL according to sociodemographic and clinical predictor variables with more than two categorical groups (Table S3). There was a significant difference in fatigue and QoL according to employment, education, marital and smoking status. Furthermore, there were significant differences in fatigue (MFI) and QoL according to CD diagnosis and living alone respectively ($P < .10$).

Multivariable analysis

Factors associated with severity of fatigue (IBD-F1 and MFI). Significant factors in univariate analyses in respect to severity of fatigue ($P < 0.10$) were examined in two separate regression models for the IBD-F1 and the MFI (see Table 2). Disease activity ($P = 0.01$) was significantly positively associated with fatigue, explaining 21%

Table 1 | Sociodemographic and clinical characteristics of study participants (n = 182)

Variable, N (%)	UC	CD	IBD-U	All IBD
N of responders	60 (33)	116 (64)	6 (3)	182
Female gender	33 (55)	68 (59)	3 (50)	104 (57)
Age, median (range), years	36.5 (20–83)	38.0 (20–80)	32.0 (22–40)	37.0 (20–83)
Education				
Up to 16	2 (3)	19 (16)	0 (0)	21 (12)
Up to 18	8 (13)	22 (19)	1 (17)	31 (17)
Higher education	50 (83)	75 (65)	5 (83)	130 (71)
Marital status				
Married/living with partner	35 (58)	76 (66)	3 (50)	115 (63)
Widowed/divorced	2 (4)	7 (6)	0 (0)	9 (5)
Single/single parent/other	23 (38)	33 (28)	3 (50)	58 (32)
Employment status				
Full time/Part time	48 (80)	72 (62)	6 (100)	126 (69)
Retired	6 (10)	12 (10)	0 (0)	18 (10)
Not working/housekeeping	6 (10)	32 (28)	0 (0)	38 (21)
Living status				
Alone	8 (13)	17 (15)	0 (0)	25 (14)
With partner/spouse/child/other relatives/friends	52 (87)	99 (85)	6 (100)	157 (86)
Smoking status				
Yes	5 (8)	8 (7)	1 (17)	14 (8)
Ex	19 (32)	30 (26)	0 (0)	49 (27)
No	36 (60)	78 (67)	5 (83)	119 (65)
Exercise status (weekly)				
>30 min aerobic exercise	39 (65)	76 (66)	2 (20)	117 (64)
<30 min aerobic exercise	21 (39)	40 (34)	4 (80)	65 (36)
Montreal classification (n = 170)				
L1 ileal		27 (16)		
L2 colonic		25 (15)		
L3 ileocolonic		62 (36)		
E1 proctitis	11 (7)			
E2 left-sided UC	24 (14)			
E3 extensive UC	21 (12)			
Years diagnosis, median (range)	8.9 (1–50)	13.7 (0.83–50)	5.2 (2–16)	12.0 (0.8–50)
Current medication				
5-ASA	43 (72)	97 (84)	3 (50)	65 (36)
Thiopurines	26 (43)	54 (47)	3 (50)	83 (46)
Methotrexate	0 (0)	4 (3)	0 (0)	4 (2)
Anti-TNF	7 (12)	54 (47)	2 (33)	63 (35)
Vedolizumab	3 (5)	3 (3)	1 (17)	7 (4)
Antibiotics	1 (2)	4 (3)	0 (0)	5 (3)
Steroids	5 (8)	11 (9)	0 (0)	16 (9)
Previous surgery	4 (7)	60 (52)	0 (0)	64 (35)
Current stoma	1 (2)	8 (7)	0	9 (5)

anti-TNF, anti-tumour necrosis factor; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; UC, ulcerative colitis; 5-ASAs, aminosalicylates.

of the variance in severity of fatigue scores. In the second block emotional, cognitive and behavioural variables were added, which significantly improved the predictive validity of the model, $F_{inc}(13, 147) = 9.78$, $P < 0.001$, explaining 54% of the variance in severity of fatigue scores. More negative fatigue perceptions were significantly associated with greater IBD-FI scores. After adjusting for psychosocial variables, disease activity

($b = 0.77$, $P = 0.18$) was no longer significantly associated with severity of fatigue ($b = 0.11$, $P = 0.15$).

Sociodemographic and clinical factors explained 24% of the variance in severity of fatigue assessed with the MFI general fatigue scale. Female gender, taking anti-TNF, disease activity and doing less than 30 min of exercise per week was associated with significantly greater fatigue scores. After adding emotional, cognitive and

Table 2 | Hierarchical regression of sociodemographic, clinical and psychosocial predictors of fatigue

B (95% CI)	IBD-F1			IBD-F2			MFI*	
	P-value	ΔR^2	B (95% CI)	P-value	ΔR^2	B (95% CI)	P-value	ΔR^2
Step 1			0.21			0.32		0.24
Sociodemographic								
Education to 16	0.62 (−1.90 to 3.13)	0.63		−3.95 (−17.64 to 9.74)	0.57	−1.34 (−3.47 to 0.80)	0.22	
Education to 18	1.67 (−0.45 to 3.80)	0.12		2.36 (−8.73 to 13.44)	0.67	−0.45 (−2.20 to 1.20)	0.61	
Employment retired	−1.83 (−4.48 to 0.82)	0.17		−4.33 (−17.57 to 8.90)	0.52	−0.52 (−2.61 to 1.57)	0.62	
Employment not work	1.22 (−0.72 to 3.15)	0.22		12.95 (2.88–23.01)	0.01	1.22 (−0.40 to 2.84)	0.14	
Female gender	1.61 (0.15–3.07)	0.03		5.32 (−2.25–12.88)	0.17	1.60 (0.40–2.80)	0.01	
Single/ S parent	−0.44 (−2.00 to 1.12)	0.58		–		–		
Divorced/ widowed	0.75 (−3.57 to 5.07)	0.73		–		–		
Clinical								
5-ASA	–			−2.29 (−10.55 to 5.97)	0.58	–		
Anti-TNF	–			11.30 (3.53–19.07)	0.01	1.86 (0.57–3.14)	0.01	
Diagnosis CD	–			–		0.78 (−0.62 to 2.18)	0.27	
Diagnosis IBD-U	–			–		1.81 (−1.42–5.05)	0.27	
Disease activity	0.27 (0.07–0.46)	0.01		2.17 (1.21 to 3.13)	<0.001	0.21 (0.06–0.36)	0.01	
Exercise <30 min	0.66 (−0.84 to 2.16)	0.38		1.98 (−6.01 to 9.96)	0.62	1.99 (0.72–3.26)	0.01	
Methotrexate	–			–		1.74 (−1.77 to 5.25)	0.33	
Smoking current	0.36 (−2.86 to 3.58)	0.82		–		–		
Smoking ex	0.21 (−1.50 to 1.91)	0.81		–		–		
Steroids	–			12.72 (−1.32 to 26.76)	0.75	–		
Thiopurines	−1.17 (−2.60 to 0.27)	0.11		–		–		
Step 2			0.54			0.73		0.54
Emotional								
Anxiety	0.04 (−0.17 to 2.56)	0.68		−0.45 (−1.35 to 0.45)	0.32	0.23 (−0.16 to 0.21)	0.81	
Depression	−0.09 (−0.32 to 0.14)	0.44		0.75 (−0.24 to 1.74)	0.13	0.13 (−0.78 to 0.34)	0.22	
Distress	0.01 (−0.01 to 0.01)	0.67		0.06 (0.01–0.11)	0.02	0.01 (−0.01 to 0.01)	0.44	
Stress	−0.06 (−0.07 to 0.19)	0.39		0.65 (0.09–1.21)	0.03	0.10 (−0.02 to 0.21)	0.10	
Cognitive								
Negative fatigue perceptions	0.28 (0.20–0.36)	<0.001		0.55 (0.12–0.78)	0.01	0.18 (0.12–0.25)	<0.001	
Catastrophising	0.01 (−0.19 to 0.21)	0.92		0.49 (−0.36 to 1.34)	0.26	−0.01 (−0.19 to 0.16)	0.88	
Damage beliefs	0.08 (−0.11 to 0.26)	0.40		−0.17 (−0.93 to 0.59)	0.65	−0.01 (−0.15 to 0.16)	0.93	
Embarrassment	−0.08 (−0.22 to 0.05)	0.20		0.06 (−0.49 to 0.62)	0.82	0.07 (−0.05 to 0.18)	0.25	
Fear avoidance	−0.07 (−0.21 to 0.08)	0.37		0.13 (−0.49 to 0.75)	0.68	0.09 (−0.03 to 0.22)	0.15	
Symptom focus	0.08 (−0.08 to 0.25)	0.34		−0.16 (−0.88 to 0.55)	0.65	0.01 (−0.14 to 0.15)	0.92	
Behavioural								
All-or-nothing behaviour	0.07 (−0.07 to 0.22)	0.31		0.86 (0.25–1.48)	0.01	−0.02 (−0.15 to 0.11)	0.71	
Avoidance behaviour	0.11 (−0.05 to 0.26)	0.17		1.31 (0.65–1.98)	<0.001	0.01 (−0.13 to 0.14)	0.98	
Daytime sleepiness	0.14 (0.01–0.28)	0.04		0.27 (−0.30 to 0.84)	0.35	0.12 (0.01–0.24)	0.04	

Figures in bold are statistically significant at $P < 0.01$; IBD-F1 Fatigue severity; IBD-F2 Fatigue impact on daily activities.

* MFI General Fatigue subscale.

ΔR^2 , adjusted R^2 ; anti-TNF, anti-tumour necrosis factor; ASA, aminosalicylates; CI, confidence interval; CD, Crohn's disease; IBD-F, inflammatory bowel disease-fatigue scale; IBD-U, Inflammatory Bowel Disease Unclassified; MFI, Multidimensional Fatigue Inventory; SEB, standard error beta.

behavioural variables and controlling for sociodemographic and clinical factors, there was a significant change in the model $F_{inc}(13, 145) = 8.78, P < 0.001$. Similarly to the IBD-F1, the fully adjusted model explained more than half (54%) of the variance in severity of fatigue. More negative fatigue perceptions were significantly associated with greater fatigue scores (MFI). Female gender, disease activity, anti-TNF and exercise were no longer significant after adjusting for psychosocial variables ($P > 0.01$).

Factors associated with impact of fatigue (IBD-F2) on individuals' lives. Significant factors in univariate analyses in respect to impact of fatigue assessed with the IBD-F2 ($P < 0.10$) were examined in a two-block hierarchical regression model (Table 2). Block 1 including sociodemographic and clinical factors (education to 16, education to 18, retired, not working/housekeeping, female gender, current 5-ASAs, current anti-TNFs, disease activity, exercise <30 min per week and current steroids) explained 32% of the variance in impact of fatigue on daily activities. Disease activity, taking anti-TNF and not working/housekeeping were all independently significantly associated with greater negative impact of fatigue on daily activities. Adding emotional, cognitive and behavioural factors in block 2 significantly improved the model $F_{inc}(13, 150) = 21.62, P < 0.001$. The model once fully adjusted for sociodemographic, clinical and psychosocial factors explained 73% of the variance in IBD-F2 impact of fatigue scores. More negative fatigue perceptions, all-or-nothing and avoidance behaviours were significantly associated with greater impact of fatigue on daily activities. After adjustment for psychosocial variables, not working, anti-TNF and higher disease activity were no longer significantly associated with impact of fatigue ($P > 0.01$).

Factors associated with IBD-specific QoL (IBDQ). Significant factors in univariate analyses in respect to IBD-specific QoL were examined in a hierarchical regression model (Table 3). Sociodemographic and clinical factors were entered in block 1. Disease activity ($P < 0.001$) and currently taking steroids ($P = 0.01$) were significantly associated with worse QoL, explaining 42% of the model. In block 2, the addition of emotional, cognitive and behavioural variables significantly increased the validity of the model, $F_{inc}(13, 141) = 7.96, P < 0.001$, with the fully adjusted model explaining 64% of the variance in QoL. Higher levels of IBD-related distress ($p = 0.01$) was significantly associated with diminished QoL. In the fully

adjusted model disease activity ($b = -1.20, P < 0.001$) and currently taking steroids ($b = -7.21, P < 0.001$) were still significantly independently associated with diminished QoL.

DISCUSSION

This study aimed to investigate factors associated with severity and impact of both fatigue on daily activities, and QoL in patients with IBD. Specifically, it investigated whether modifiable emotional, cognitive and behavioural factors, shown to be associated with fatigue in other long-term conditions,^{33, 35, 84} were also related to fatigue in patients with IBD. Potentially identifying parallels and drawing from existing treatment models in other conditions, can aid in uncovering processes of fatigue that can be applied trans-diagnostically across different conditions,^{85–87} and ultimately in synthesising new constructs to target in intervention research in IBD.³¹ The results of the study showed emotional, cognitive and behavioural factors were associated with fatigue and QoL above and beyond the influence of sociodemographic and clinical factors. Negative fatigue perceptions were significantly associated with severity of fatigue. Negative fatigue perceptions, all-or-nothing and avoidance behaviours were significantly associated with impact of fatigue. Higher levels of IBD-related distress were significantly associated with worse QoL.

Disease activity was the only clinical factor consistently independently associated with severity and impact of fatigue and QoL. While some factors such as female gender, anti-TNFs, doing less than 30 min of exercise per week and not being in employment were significantly associated with severity and impact of fatigue in univariate analysis, the associations were no longer significant in the fully adjusted multivariable regression analysis. Finally, disease activity together with currently taking steroids was significantly associated with worse QoL in both partly and fully adjusted models.

In line with findings from other clinical out-patient¹³ and population-based¹¹ studies, the results from the present study confirmed disease activity as the most consistent independent factor related to fatigue and QoL. This indicates the management of active disease, through adequate medical and/or surgical therapy, as the first line of intervention for patients with IBD-fatigue.¹⁸ In addition, the study corroborates recent findings from longitudinal observational findings suggesting that anti-TNF use is linked to more severe fatigue¹² and that cessation of biologic therapy is associated with a reduction in fatigue.¹³ It is possible that biologics have already been efficacious in managing the inflammation and potentially improving

Table 3 | Hierarchical of sociodemographic, clinical and psychosocial predictors of QoL

	IBDQ*	
B (95% CI)	P-value	ΔR^2
Step 1		
0.42		
Sociodemographic		
Education up to 16	1.28 (−5.46 to 8.05)	0.71
Education up to 18	0.74 (−4.42 to 5.91)	0.78
Employment retired	−1.47 (−8.88 to 5.94)	0.69
Employment not working/housekeeping	−2.86 (−7.72 to 2.01)	0.25
Female gender	−2.10 (−5.77 to 1.56)	0.26
Living alone	6.28 (−0.27 to 12.83)	0.06
Living single parent	−4.85 (−19.01 to 9.31)	0.50
Single/Single parent/other	−2.57 (−7.38 to 2.24)	0.29
Widowed/divorced	−1.20 (−11.77 to 9.36)	0.82
Clinical		
Disease activity	−1.86 (−2.35 to −1.36)	<0.001
Exercise <30 min	−0.07 (−3.85 to 3.70)	0.97
Methotrexate	−5.99 (−17.67 to 5.69)	0.31
Platelets	−0.02 (−0.04 to 0.01)	0.11
Smoking current	2.20 (−5.24 to 9.64)	0.56
Smoking ex	1.96 (−2.21 to 6.14)	0.36
Steroids	−10.16 (−16.98 to −3.35)	0.01
Thiopurines	1.50 (−2.10 to 5.11)	0.41
Step 2		
0.64		
Emotional		
Anxiety	−0.40 (−0.94 to 0.15)	0.15
Depression	0.05 (−0.51 to 0.61)	0.85
Distress	−0.05 (−0.09 to −0.02)	0.01
Stress	−0.08 (−0.42 to 0.26)	0.64
Cognitive		
Negative fatigue perceptions	−0.01 (−0.21 to 0.19)	0.89
Catastrophising	−0.55 (−1.10 to .01)	0.05
Damage beliefs	−0.17 (−0.71 to 0.38)	0.54
Embarrassment	−0.03 (−0.39 to 0.32)	0.85
Fear avoidance	−0.18 (−0.58 to 0.23)	0.40
Symptom focus	0.32 (−0.14 to 0.79)	0.17
Behavioural		
All-or-nothing behaviour	−0.30 (−0.67 to 0.06)	0.11
Avoidance behaviour	−0.05 (−0.51 to 0.61)	0.83
Daytime sleepiness	0.07 (−0.29 to 0.43)	0.70
Figures in bold are statistically significant at $P < 0.01$.		
ΔR^2 , adjusted R^2 ; ASA, aminosalicylates; CI, confidence interval; CD, Crohn's Disease; IBDQ, Inflammatory Bowel Disease Questionnaire; SEB, standard error beta.		
* The IBDQ total score is made up from the individual subscales.		

Figures in bold are statistically significant at $P < 0.01$.

ΔR^2 , adjusted R^2 ; ASA, aminosaliclates; CI, confidence interval; CD, Crohn's Disease; IBDQ, Inflammatory Bowel Disease Questionnaire; SEB, standard error beta.

* The IBDQ total score is made up from the individual subscales.

fatigue at the point of cessation.⁸⁸ This finding is in contrast with pharmacological trials presenting a reduction in fatigue symptoms in patients taking infliximab^{19, 21} and adalimumab.⁸⁹ However, patients taking anti-TNFs may have more severe and/or active disease, potentially suggesting disease activity as a confounding variable in this relationship.⁹⁰

Consistent with other studies,^{14, 17, 91} no significant correlations were found between fatigue and clinical

factors known to predict fatigue such as anaemia^{14–16} and iron deficiency.⁹² This lack of association has a number of possible explanations. Patients were recruited from tertiary referral centres where disease is closely monitored and managed through routine blood tests and only 17% were anaemic. Extensive missing data for ferritin (41%) and B12 (42%) levels may have limited the ability to draw conclusions on these parameters. Overall, these findings add to the evidence suggesting that,

Table 4 | Summary of factors associated with severity and impact of fatigue as measured by the IBD-F1 and IBD-F2

	IBD-F1 (95% CI)	IBD-F2 (95% CI)
Sociodemographic and clinical		
Female gender	1.61 (0.15–3.07), $P = 0.03$	NS
Employment not working/housekeeping	1.22 (–0.72 to 3.15), $P = 0.22$	12.95 (2.88–23.01), $P = 0.01$
Disease activity	0.27 (0.07–0.46), $P = 0.01$	2.17 (1.21–3.13), $P < 0.001$
Anti-TNF	–	11.30 (3.53–19.07), $P = 0.01$
Psychosocial		
Distress	NS	0.06 (0.01–0.11), $P = 0.02$
Stress	NS	0.65 (0.09–1.21), $P = 0.03$
Negative fatigue perceptions	0.28 (0.20–0.36), $P < 0.001$	0.55 (0.12–0.78), $P = 0.01$
All-or-nothing behaviour	NS	0.86 (0.25–1.48), $P = 0.01$
Avoidance behaviour	NS	1.31 (0.65–1.98), $P < 0.001$
Daytime sleepiness	0.14 (0.01–0.28), $P < 0.04$	NS

NS, not significant at $P < 0.01$.

Anti-TNF, anti-tumour necrosis factor; CI, confidence interval; IBD-F, Inflammatory Bowel Disease-Fatigue Scale.

despite centrality of anaemia in fatigue symptoms,⁹³ there is a considerable proportion of patients where fatigue cannot be explained by clinical factors alone, and employment of non-pharmacological management may be required once disease activity has been addressed.

The bidirectional link between depression and fatigue in patients with IBD^{9, 13} has been previously reported. Data from this study highlight the importance of other relatively unexplored psychosocial factors in the IBD-fatigue. Indeed, evidence from this study and studies in other long-term condition^{33, 94} suggest that individuals with more negative perceptions about their fatigue, that is, feeling of not having control over their symptoms, and who engage in maladaptive behavioural coping strategies (daytime naps) will experience higher levels of fatigue. Likewise, the associations between negative perceptions of fatigue, avoidance and all-or-nothing behaviours and impact of fatigue (measured by the IBD-F2),⁵³ may further influence the coping strategies patients employ.⁹⁵ While various clinical and sociodemographic factors may go some way to account for presence and severity of fatigue, they cannot fully explain it. Findings from this study indicate that patients' subjective interpretation and responses to symptoms of fatigue, may determine its impact on their lives.

Evidence from other chronic conditions, where fatigue is one of the symptoms, for example multiple sclerosis⁴⁵ or cancer,^{96, 97} highlight the necessity for a paradigm shift in its management from strategies solely or predominantly focused on physical health towards an integrated approach assessing and targeting a range of factors according to patients' needs.⁹⁸ In instances where

the fatigue is evidently related to a disease flare or other clinical problems, medical or surgical therapy may be beneficial. However, where there is no apparent explanation for fatigue, exploring psychosocial factors contributing to the onset and perpetuation of fatigue may be of value.⁹⁹ It is important to regularly assess IBD patients for fatigue and to try and identify its possible cognitive-behavioural associates. This could be the starting point in employing a holistic and systematic strategy for fatigue management.³

Limitations

The findings of the study should be considered in the light of several limitations. Due to the cross-sectional study design, causality between the different factors and fatigue cannot be inferred. Longitudinal designs would allow for more robust temporal associations between clinical and psychosocial factors to be assessed, together with an analysis of mediating factors. The use of patient self-report DAI scores when clinician-reported outcomes were not available may have resulted in incomplete or inaccurate data on remission status.¹⁰⁰ Although self-reported DAIs are often used in research studies,^{10, 11} nevertheless, it is best practice for clinicians to complete them after obtaining information from the patients.¹⁰¹ Furthermore, the extensive missing data for faecal calprotectin meant that this could not be utilised as an indicator of disease activity for the entire sample. Similarly, the study was not funded for additional blood tests unless they were indicated clinically. The collection of bloods upon questionnaire completion in future studies would minimise issues with missing clinical data

encountered in this study. The significant correlation between QoL, fatigue and psychosocial factors may indicate a cross-validation between overlapping measures, longitudinal findings are therefore needed to reach more definitive conclusions on fatigue pathways. Recruitment from clinics and biologic infusion units at tertiary referral centres may indicate a sub-set of the IBD population, where the disease is closely monitored and well-managed. The moderate sample size precluded exploration of the differences according to diagnosis phenotype, potentially limiting the generalisability of the findings specifically to UC and CD populations.

CONCLUSIONS

The identification of psychosocial variables that predict fatigue over and above sociodemographic and clinical variables, emphasises the importance of conducting research on factors potentially amenable to modification. The study findings indicate that emotional and behavioural factors and patients' negative fatigue perceptions, may be the key factors to be addressed, possibly through psychological therapy. Further exploration of these factors in longitudinal and intervention studies may help to develop cognitive-behavioural models of fatigue management.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Univariate correlations between fatigue, QoL and sociodemographic, clinical and psychosocial predictor variables ($n = 182$).

Table S2. Univariate independent samples *t*-tests of differences between fatigue and QoL according to sociodemographic and clinical predictor variables ($n = 182$).

Table S3. Univariate one-way between groups ANOVAS of differences between fatigue and QoL according to sociodemographic and clinical predictor variables ($n = 182$).

AUTHORSHIP

Guarantor of the article: M. Artom.

Author contributions: MA, WCD, CN, JS were responsible for the conception of the study; MA was responsible for data collection; MA and TM were responsible for data analysis; MA was responsible for interpretation of the data and drafting the manuscript. All authors have read, commented and approved on the final version of this article and are responsible for its content.

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

Declaration of funding interests: The study was part of a PhD project funded by King's College London.

REFERENCES

- Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manage* 2009; **37**: 107–28.
- van Langenberg DR, Papandony MC, Gibson PR. Sleep and physical activity measured by accelerometry in Crohn's disease. *Aliment Pharmacol Ther* 2015; **41**: 991–1004.
- Kreijne JE, Lie MRKL, Vogelaar L, van der Woude CJ. Practical guideline for fatigue management in inflammatory bowel disease. *J Crohns Colitis* 2015; **10**: 105–11.
- Czuber-Dochan W, Ream E, Norton C. Review article: description and management of fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**: 505–16.
- Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004; **56**: 157–70.
- Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev* 2006; **10**: 63–76.
- Czuber-Dochan W, Dibley LB, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: an exploratory study. *J Adv Nurs* 2013; **69**: 1987–99.
- Czuber-Dochan W, Norton C, Bredin F, Darvell M, Nathan I, Terry H. Healthcare professionals' perceptions of fatigue experienced by people with IBD. *J Crohn's Colitis* 2014; **8**: 835–44.
- Norton C, Czuber-Dochan W, Bassett P, et al. Assessing fatigue in inflammatory bowel disease: comparison of three fatigue scales. *Aliment Pharmacol Ther* 2015; **42**: 203–11.
- Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014; **39**: 811–22.
- Graff LA, Clara I, Walker JR, et al. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clin Gastroenterol Hepatol* 2013; **11**: 1140–6.
- Vogelaar L, van't Spijker A, van Tilburg AJ, Kuipers EJ, Timman R, van der Woude CJ. Determinants of fatigue in Crohn's disease patients. *Eur J Gastroenterol Hepatol* 2013; **25**: 246–51.
- van Langenberg DR, Gibson PR. Factors associated with physical and cognitive fatigue in patients with Crohn's disease: a cross-sectional and longitudinal study. *Inflamm Bowel Dis* 2014; **20**: 115–25.
- Bager P, Befrits R, Wikman O, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther* 2012; **35**: 133–41.
- Jelsness-Jørgensen LP, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis* 2011; **17**: 1564–72.

16. Yoo S, Jung YS, Park JH, et al. Fatigue severity and factors associated with high fatigue levels in Korean patients with inflammatory bowel disease. *Gut Liv* 2014; **8**: 148.
17. Grimstad T, Norheim KB, Isaksen K, et al. Fatigue in newly diagnosed inflammatory bowel disease. *J Crohns Colitis* 2015; **9**: 725–30.
18. Artom M, Czuber-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. *J Crohns Colitis* 2016; **10**: 860–9.
19. Lichtenstein GR, Bala M, Han C, DeWoody K, Schaible T. Infliximab improves quality of life in patients with Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 237–43.
20. Garcia-Vega E, Fernandez-Rodriguez C. A stress management programme for Crohn's disease. *Behav Res Ther* 2004; **42**: 367–83.
21. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? *W J Gastroenterol* 2007; **13**: 2089–93.
22. Costantini A, Pala MI. Thiamine and fatigue in inflammatory bowel diseases: an open-label pilot study. *J Altern Complement Med* 2013; **19**: 704–8.
23. Vogelaar L, van't Spijker A, Timman R, et al. Fatigue management in patients with IBD: a randomised controlled trial. *Gut* 2014; **63**: 911–8.
24. Salleron J, Danese S, D'Agay L, Peyrin-Biroulet L. Effectiveness research in inflammatory bowel disease: a necessity and a methodological challenge. *J Crohns Colitis* 2016; **10**: 1096–102.
25. Jackson BD, Gray K, Knowles SR, De Cruz P. EHealth technologies in inflammatory bowel disease: a systematic review. *J Crohn's Colitis* 2016; **10**: 1103–21.
26. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; **60**: 571–607.
27. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014; **12**: 1246–56.e6.
28. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015; **110**: 1324–38.
29. Vogelaar L, van't Spijker A, Vogelaar T, et al. Solution focused therapy: a promising new tool in the management of fatigue in Crohn's disease patients: psychological interventions for the management of fatigue in Crohn's disease. *J Crohns Colitis* 2011; **5**: 585–91.
30. Kalaitzakis E, Carlsson E, Josefsson A, Bosaeus I. Quality of life in short-bowel syndrome: impact of fatigue and gastrointestinal symptoms. *Scand J Gastroenterol* 2008; **43**: 1057–65.
31. Banovic I, Glibert D, Jebrane A, Cosnes J. Diagnostic profiles determined by the CART procedure: IBD patients and fatigue. *J Health Psychol* 2011; **17**: 500–8.
32. Banovic I, Glibert D, Jebrane A, Cosnes J. Personality and fatigue perception in a sample of IBD outpatients in remission: a preliminary study. *J Crohns Colitis* 2012; **6**: 571–7.
33. Skerrett TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *J Psychosom Res* 2006; **61**: 587–93.
34. van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res* 2006; **61**: 583–5.
35. Chilcot J, Moss-Morris R, Artom M, et al. Psychosocial and clinical correlates of fatigue in haemodialysis patients: the importance of patients' illness cognitions and behaviours. *Int J Behav Med* 2015; **23**: 271–81.
36. Zalai D, Sherman M, McShane K, Shapiro CM, Carney CE. The importance of fatigue cognitions in chronic hepatitis C infection. *J Psychosom Res* 2015; **78**: 193–8.
37. Czuber-Dochan W. Exploring fatigue in inflammatory bowel disease as experienced by individuals – a descriptive phenomenological study. Unpublished PhD thesis, 2015, King's College London.
38. Leventhal H, Meyer D, Nerenz D. The common sense representation of illness danger. *Contrib Med Psychol* 1980; **2**: 7–30.
39. Knowles S, Wilson J, Connell W, Kamm M. Preliminary examination of the relations between disease activity, illness perceptions, coping strategies, and psychological morbidity in Crohn's disease guided by the common sense model of illness. *Inflamm Bowel Dis* 2011; **17**: 2551–7.
40. van der Have M, Brakenhoff LK, van Erp SJ, et al. Back/joint pain, illness perceptions and coping are important predictors of quality of life and work productivity in patients with inflammatory bowel disease: a 12-month longitudinal study. *J Crohn's Colitis* 2015; **9**: 276–83.
41. van der Have M, Oldenburg B, Kaptein AA, et al. Non-adherence to anti-TNF therapy is associated with illness perceptions and clinical outcomes in outpatients with inflammatory bowel disease: results from a prospective multicentre study. *J Crohns Colitis* 2016; **10**: 549–55.
42. Broadbent E, Ellis CJ, Thomas J, Gamble G, Petrie KJ. Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. *J Psychosom Res* 2009; **67**: 17–23.
43. Petrie KJ, Perry K, Broadbent E, Weinman J. A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *Br J Health Psychol* 2012; **17**: 74–84.
44. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med* 2008; **70**: 205–13.
45. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. *Behav Res Ther* 2012; **50**: 415–21.
46. Knoop H, van Kessel K, Moss-Morris R. Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychol Med* 2012; **42**: 205–13.
47. Christensen SS, Frostholm L, Ørnbøl E, Schröder A. Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes. *J Psychosom Res* 2015; **78**: 363–70.
48. Reme S, Stahl D, Kennedy T, Jones R, Darnley S, Chalder T. Mediators of change in cognitive behaviour therapy and mebeverine for irritable bowel syndrome. *Psychol Med* 2011; **41**: 2669–79.
49. Harvey R, Bradshaw J. A simple index of Crohn's-disease activity. *The Lancet* 1980; **315**: 514.
50. Walmsley R, Ayres R, Pounder R, Allan R. A simple clinical colitis activity index. *Gut* 1998; **43**: 29–32.
51. Evertsz FB, Hoeks CC, Nieuwkerk PT, et al. Development of the patient Harvey Bradshaw index and a comparison with a clinician-based Harvey Bradshaw index assessment of

- Crohn's disease activity. *J Clin Gastroenterol* 2013; **47**: 850–6.
52. Everts FB, Nieuwkerk PT, Stokkers PC, et al. The Patient Simple Clinical Colitis Activity Index (P-SCCAI) can detect Ulcerative Colitis (UC) disease activity in remission: a comparison of the P-SCCAI with clinician-based SCCAI and biological markers. *J Crohns Colitis* 2013; **7**: 890–900.
 53. Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *J Crohns Colitis* 2014; **8**: 1398–406.
 54. Smets E, Garssen B, Bonke Bd, De Haes J. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; **39**: 315–25.
 55. van Tubergen A, Coenen J, Landewé R, et al. Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. *Arthritis Care Res* 2002; **47**: 8–16.
 56. d'Elia HF, Rehnberg E, Kvist G, Ericsson A, Konttinen Y, Mannnerkorpi K. Fatigue and blood pressure in primary Sjögren's syndrome. *Scand J Rheumatol* 2008; **37**: 284–92.
 57. Ericsson A, Bremell T, Mannnerkorpi K. Usefulness of multiple dimensions of fatigue in fibromyalgia. *J Rehab Med* 2013; **45**: 685–93.
 58. Agresti A, Kateri M. *Categorical Data Analysis*. Berlin, Heidelberg: Springer, 2011.
 59. Guyatt G, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel. *Gastroenterology* 1989; **96**: 804–10.
 60. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361–70.
 61. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; **24**: 385–96.
 62. Woodward S, Dibley L, Coombes S, et al. Identifying disease-specific distress in patients with inflammatory bowel disease. *Br J Nurs* 2016; **25**: 649–60.
 63. Haug TT, Mykletun A, Dahl AA. The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-II study. *Psychosom Med* 2004; **66**: 845–51.
 64. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *J Psychosom Res* 2002; **52**: 69–77.
 65. Woodward S, Dibley L, Coombes S, et al. Identifying disease-specific distress in patients with inflammatory bowel disease. *Br J Nurs* 2016; **25**: 649–60.
 66. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006; **60**: 631–7.
 67. Moss-Morris R, Weinman J, Petrie K, Horne R, Cameron L, Buick D. The revised illness perception questionnaire (IPQ-R). *Psychol Health* 2002; **17**: 1–16.
 68. Petriček G, Vrcić-Keglević M, Vuletić G, Cerovečki V, Ozvacić Z, Murgić L. Illness perception and cardiovascular risk factors in patients with type 2 diabetes: cross-sectional questionnaire study. *Croat Med J* 2009; **50**: 583–93.
 69. Wilson ER, Wisely JA, Wearden AJ, Dunn KW, Edwards J, Tarrier N. Do illness perceptions and mood predict healing time for burn wounds? A prospective, preliminary study. *J Psychosom Res* 2011; **71**: 364–6.
 70. Powell H, McCaffery K, Murphy VE, et al. Psychosocial variables are related to future exacerbation risk and perinatal outcomes in pregnant women with asthma. *J Asthma* 2013; **50**: 383–9.
 71. van Oort L, Schröder C, French D. What do people think about when they answer the Brief Illness Perception Questionnaire? A 'think-aloud' study. *Br J Health Psychol* 2011; **16**: 231–45.
 72. Chilcot J, Moss-Morris R. Changes in illness-related cognitions rather than distress mediate improvements in irritable bowel syndrome (IBS) symptoms and disability following a brief cognitive behavioural therapy intervention. *Behav Res Ther* 2013; **51**: 690–5.
 73. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**: 540–5.
 74. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. *J Sleep Res* 2000; **9**: 5–11.
 75. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002; **7**: 147–77.
 76. Barnard J, Meng X-L. Applications of multiple imputation in medical studies: from AIDS to NHANES. *Stat Methods Med Res* 1999; **8**: 17–36.
 77. Faul F, Erdfelder E, Lang A-G, Buchner A. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Meth* 2007; **39**: 175–91.
 78. Cunningham JB, McCrum-Gardner E. Power, effect and sample size using GPower: practical issues for researchers and members of research ethics committees. *Evidence Based Midwifery* 2007; **5**: 132–7.
 79. Belsey DA. A guide to using the collinearity diagnostics. *Comput Sci Econ Manage* 1991; **4**: 33–50.
 80. Belsey DA, Kuh E, Welsch RE. *Regression Diagnostics: Identifying Influential Data and Sources of Collinearity*. Hoboken, New Jersey: John Wiley & Sons, 2005.
 81. Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. New York, NY: Cambridge University Press, 2006.
 82. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Roy Stat Soc B (Methodological)* 1995; **57**: 289–300.
 83. Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis* 2015; **9**: 211–22.
 84. van Hoogmoed D, Fransen J, Bleijenberg G, van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology* 2010; **49**: 1294–302.
 85. Clark DA, Taylor S. The transdiagnostic perspective on cognitive-behavioral therapy for anxiety and depression: new wine for old wineskins? *J Cogn Psychoth* 2009; **23**: 60–6.
 86. Newby JM, McKinnon A, Kuyken W, Gilbody S, Dalgleish T. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. *Clin Psychol Rev* 2015; **40**: 91–110.
 87. Windgassen S, Goldsmith K, Moss-Morris R, Chalder T. Establishing how psychological therapies work: the importance of mediation analysis. *J Ment Health* 2015; **25**: 93–9.
 88. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 537.
 89. Loftus EV, Feagan BG, Colombel J-F, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008; **103**: 3132–41.
 90. Opheim R, Fagermoen MS, Bernklev T, Jelsness-Jørgensen L-P, Moum B. Fatigue interference with daily living

- among patients with inflammatory bowel disease. *Qual Life Res* 2014; **23**: 707–17.
91. Goldenberg BA, Graff LA, Clara I, *et al.* Is iron deficiency in the absence of anemia associated with fatigue in inflammatory bowel disease. *Am J Gastroenterol* 2013; **108**: 1392–7.
 92. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 599–610.
 93. Bager P, Befrits R, Wikman O, *et al.* The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. *Scand J Gastroenterol* 2011; **46**: 304–9.
 94. Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. *Clin Psychol Rev* 2007; **27**: 781–97.
 95. Hagger MS, Orbell S. A meta-analytic review of the common-sense model of illness representations. *Psychol Health* 2003; **18**: 141–84.
 96. Foster C, Calman L, Grimmett C, *et al.* Managing fatigue after cancer treatment: development of RESTORE, a web-based resource to support self-management. *Psycho-Oncology* 2015; **24**: 940–9.
 97. Myall M, May CR, Grimmett C, *et al.* RESTORE: an exploratory trial of a web-based intervention to enhance self-management of cancer-related fatigue: findings from a qualitative process evaluation. *BMC Med Inform Decis Mak* 2015; **15**: 94.
 98. Gracie DJ, Williams CJM, Sood R, *et al.* Poor correlation between clinical disease activity and mucosal inflammation, and the role of psychological comorbidity, in inflammatory bowel disease. *Am J Gastroenterol* 2016; **111**: 541–51.
 99. Farrell D, Savage E, Norton C, Jelsness-Jørgensen LP, Czuber-Dochan W, Artom M. Interventions for fatigue in inflammatory bowel disease. *Cochrane Library* 2015; doi: 10.1002/14651858.CD012005.
 100. Walsh AJ, Ghosh A, Brain AO, *et al.* Comparing disease activity indices in ulcerative colitis. *J Crohns Colitis* 2014; **8**: 318–25.
 101. Turner D, Griffiths AM, Mack D, *et al.* Assessing disease activity in ulcerative colitis: patients or their physicians? *Inflamm Bowel Dis* 2010; **16**: 651–6.

4.1 Cross-sectional study design

In observational studies, the investigator observes and evaluates the results that occur without an intervention and does not allocate or control the exposure. The main types of observational studies are cross-sectional, cohort, case-control and case report studies (DiPietro, 2010). Cross-sectional studies are carried out at one time point or over a limited period in order to provide a snapshot of the outcome and the characteristics associated with it (Levin, 2006). They are a type of descriptive observational study which is commonly utilised either to determine prevalence or consider possible associations between exposure and outcome. In the latter case, independent and dependent variables are identified in a given population and then the associations between them are determined. Cross-sectional studies are a useful way of identifying associations that can subsequently be more rigorously tested in an analytic design such as an RCT. Advantages of cross-sectional studies are that they are relatively quick and as there is no follow-up fewer resources are required to run the study. Furthermore, although data are collected only once, multiple outcomes can be studied at the same time (Mann, 2003). Additionally, compared to longitudinal studies where loss to follow-up is common, this is not a problem in cross-sectional study design (Levin, 2006). For the purposes of this PhD project, the use of a cross-sectional study allowed for the assessment of fatigue and its association with multiple clinical and psychosocial outcomes at one point in time and yielded data needed to inform the intervention development.

4.2 Study questionnaires

Numerous questionnaires were selected to measure a number of clinical and psychosocial factors possibly linked to IBD-fatigue. The study questionnaires were presented to participants grouped in a booklet (Appendix X).

4.2.1 IBD-Fatigue Scale (IBD-F)

The IBD-F Scale (Czuber-Dochan et al., 2014a) aims to assess IBD-specific fatigue. The questionnaire has three sections. Section I consists of five questions assessing frequency and severity of fatigue; section II consists of 30 questions rating the experience and impact of fatigue; and section III is a free-text section asking for patients' comments and additional issues related to fatigue. Higher scores reflect higher levels of fatigue. Initial validation of the measure suggested that the questionnaire had good face and content validity, acceptable to excellent test-retest stability and a high degree of internal consistency (Czuber-Dochan et al., 2014a). Both sections of the IBD-F have been found to be significantly correlated with widely utilised fatigue scales in IBD (Norton et al., 2015). To date, the scale has been translated into a number of languages: Danish (Bager et al., 2017), Polish, Spanish, American English, Greek, Chinese, and is currently being tested in tertiary referral centres in different countries.

The scale was chosen for the current study as it was developed by conducting in-depth interviews with participants with IBD, in order to gain insight into their experience. The use of an IBD-specific scale can be utilised to represent issues of specific importance to people with IBD-fatigue. Indeed, the different manifestations and the wide range of mechanisms underlying fatigue make it difficult for one scale to be appropriate for measuring fatigue in all disease groups (Dittner et al., 2004). Furthermore, aside from measuring frequency and severity of fatigue, IBD-F allowed for the understanding of the effects of fatigue on patients' lives, hence assessing the problems that they attribute to fatigue. The perception of the impact of fatigue can vary greatly from person to person. As fatigue and QoL are subjective states, it may be critical to select an instrument that measures not only fatigue, but fatigue in the context of other dimensions of well-being, such as physical, functional, social, and emotional well-being (Yellen et al., 1997). Additionally, the IBD-F asks patients about the fatigue experienced in the "past two weeks". Fatigue experienced "in the past week" was most commonly used by other scales. This is a longer timeframe compared to most fatigue scales utilised in studies of non-cancer gastrointestinal disorders (Han et al., 2016), thus allowing for a more extensive view of the patients' experience to be captured. Likewise, it can be hypothesised that a longer timeframe may reflect a general state of fatigue rather than acute episodes that may not be representative of patients in remission (Stover et al., 2013).

The IBD-F has been criticised for being too long to be used in clinical practice. Lengthy measures are likely to be difficult to implement consistently in clinical practice and in RCTs, for which parsimony is a desirable property (Ju et al., 2017). Nonetheless, strong correlations between sections I and II suggest that section I may be used as a screening tool alone (Vestergaard et al., 2017). Following guidance by Whitehead (2009), for the purposes of this study, the final choice of using the whole scale represented a compromise between the detail required and the practical issues of completion. As Patient and Public Involvement responses indicated that the questionnaire was acceptable to patients, both sections were utilised in order to gather valuable information on the severity and impact of IBD-fatigue on patients' daily activities. Furthermore, it is possible that the longer time-frame of the scale may increase the levels of recall bias that are inherent to self-report questionnaires (Heine et al., 2016). Indeed, individuals have been found to focus on the high levels of a phenomenon when assessed using recall questionnaires (Stone et al., 2005). As such, findings from the IBD-F should be interpreted in light of these limitations.

4.2.2 Multidimensional Fatigue Inventory (MFI)

The MFI (Smets et al., 1995) is the most commonly used scale to measure fatigue in IBD (Czuber-Dochan et al., 2013a). It is a 20-item self-assessment instrument designed to measure five dimensions of fatigue (physical fatigue, mental fatigue, general fatigue, reduced activity and motivation). Each dimension comprises four questions with scores ranging from 4 to 20 per dimension, with higher scores indicating greater fatigue. The "general fatigue" subscale is

commonly referenced as the primary fatigue descriptor, as opposed to using a total MFI scale score. Different cut-off points for fatigue have been adopted to delineate high or problematic fatigue in IBD. Most studies have utilised a cut-off of 13 (Goldenberg et al., 2013) on the basis of the ninth percentile of the score in a healthy control group (Graff et al., 2013). The MFI has shown good psychometric properties in patients with long-term conditions such as cancer (Tian and Hong, 2013) and it has recently been validated with patients with IBD (Norton et al., 2015).

The MFI was chosen to be used in conjunction with the more recently developed IBD-F as the latter is an IBD-specific instrument. The MFI can assess different aspects of fatigue and it enables a comparison with healthy controls and other conditions. Having a common metric for fatigue across chronic health conditions can enhance the interpretability of fatigue across clinical research studies (Cella et al., 2016). The IBD-F is a relatively recently developed scale, hence currently data on its use is not extensive. Therefore the addition of a scale which has been used extensively both in IBD (Czuber-Dochan et al., 2013a) and other long-term conditions (Ballesio et al., 2017) can aid in avoiding information biases that might lead to incorrect interpretation of the data (Anthoine et al., 2014). It was decided that a multidimensional fatigue-specific instrument would help to better characterise fatigue in the study sample. Fatigue is a generic concept and it was not specifically constructed with a particular diagnosis in mind (Lerdal and Kottorp, 2011). Indeed, generic instruments can provide a useful brief index of fatigue in the context of broader health outcome (Dittner et al., 2004). They can also facilitate the documentation of commonalities and differences in relation to the severity and impact of fatigue across conditions (Hjollund et al., 2007, Whitehead et al., 2016).

4.2.3 United Kingdom Inflammatory Bowel Disease Questionnaire (UK IBDQ)

The IBDQ (Cheung et al., 2000) is the British version of the McMaster IBDQ (Guyatt et al., 1989). It has 30 items, each scored in the range 1 to 4, with a summary score between 30 and 120. A low score indicates poor QoL. Initial findings have supported the reliability, validity, reproducibility and responsiveness of the UK version of the questionnaire. The questionnaire has been found acceptable to patients in the UK. It enhances the precision of some of the questions in the McMaster IBDQ, improves the readability of the questionnaire, removes items that do not provide useful information and simplifies the response categories. The IBDQ was tested and validated for the first time in 1994 in a multicentre clinical trial that reported a correlation between the IBDQ and disease activity (Irvine et al., 1994). Findings have supported its validity, reliability and its acceptability to patients with IBD cross-culturally across several cultural and linguistic milieus (Lopez-Vivancos et al., 1999, Masachs et al., 2007, Ren et al., 2007, Ciccocioppo et al., 2011, Maleki et al., 2015). The IBDQ is now the most established QoL measure in the IBD literature (Alrubaiy et al., 2015).

The IBDQ was chosen as it was developed with patients with IBD, it therefore reflects the concerns of the patients themselves about the impact of their disease on their life-style and QoL. Members of our Patient and Public Involvement group voted 15:2 in favour of the UK version when compared with the original version, stating “choices are more straightforward”. As fatigue has been found to be strongly associated with poor QoL in IBD (Cohen et al., 2014), exploring the association between modifiable factors and QoL was deemed as an important aspect to consider in the study. Indeed, the identification of factors associated with both fatigue and QoL could ultimately lead to the development of interventions that could improve both fatigue and QoL in patients with IBD.

4.2.4 Hospital Anxiety and Depression Scale (HADS)

The HADS (Zigmond and Snaith, 1983) is a widely used self-report instrument for assessing depression and anxiety in patients with medical illnesses. It has two subscales, anxiety and depression, each consisting of seven items. The two subscales are scored separately and higher scores indicate higher anxiety and depression respectively. The HADS was chosen for the current study because, as opposed to other measures, it was originally developed for physically ill patients and no items assessing somatic symptoms are included. In studies across different conditions (Bjelland et al., 2002) and in IBD-specifically (Kjærgaard et al., 2014) its internal consistency has been found to be high. For the HADS-total the optimal cut-off was found to be ≥ 9 (sensitivity 85%, specificity 81%) and for HADS-A (anxiety) and the HADS- D (depression), the optimal cut-off were at ≥ 4 (sensitivity 85%, specificity 79%) (Kjærgaard et al., 2014). The HADS is the most common measurement tool for the measurement of anxiety and depression in IBD (Neuendorf et al., 2016).

However, the HADS has not yet been validated specifically for use in the IBD population. Moreover, the scale contains a number of symptom items including feeling slowed down, abdominal sensations and worry, which are commonly experienced by patients with IBD as part of their core IBD symptoms and as a normal psychological adjustment to such a diagnosis (Farrell et al., 2015a). There may hence be a risk of criterion contamination between IBD symptomology with anxiety and depressive symptoms measured by the HADS (Hopkins, 2017). Findings of the HADS in patients with IBD should thus be interpreted with caution and validation of its psychometric properties with the IBD population is warranted. Despite these limitations the HADS was chosen for the present study as it has been extensively utilised in both standard medical practice and health-related research and it performs better than other scales in patients from non-psychiatric hospital clinics (Bjelland et al., 2002). Furthermore, the scale only takes 2 to 5 minutes to complete and it has been shown to be acceptable to the population for which it is designed (Snaith, 2003).

4.2.5 *Epworth Sleepiness Scale (ESS)*

The ESS (Johns, 1991) is utilised to measure a subject's level of daytime sleepiness and provides a practical assessment of interference during the day (Johns, 2000). From a clinical point of view, this is relevant in that it helps to determine the presence of pathology or simply predict whether sleep onset is likely to occur at inappropriate times (Shen et al., 2006). The questionnaire asks subjects to rate their chance of falling asleep or dozing on a scale of 0 to 3 in eight soporific situations, ranging from 'Lying down to rest in the afternoon when circumstances permit' to 'in a car while stopped for a few minutes in traffic'. A total score from 0 to 24 is determined, with values over 10/11 indicating abnormal or pathological sleepiness. The ESS is a major instrument for measuring sleep outcomes in RCTs (Giles et al., 2006) and it is one of the most widely used tools for the assessment of sleepiness. It also has the advantages of being easy to use, cost-effective (Chervin, 2003) and able to quickly summarise events occurring over a long period (Ali and Orr, 2014).

The ESS has been criticised for being a subjective rating of sleep propensity in daily life and only covering one specific aspect of the multi-dimensional concept of sleepiness. The questionnaire has a single factor structure and it contains only one item relating to each situation where patients could fall asleep (Cluydts et al., 2002, Smith et al., 2008, Olaithe et al., 2013). However, there is no gold standard for the measurement of outcomes in sleep and sleep-related conditions due to the heterogeneous impacts of these conditions on QoL (Kaambwa et al., 2016). Due to the huge body of findings on the ESS and the knowledge of its strengths and limitations, utilising the ESS as an assessment tool for evaluating sleepiness has thus been advised to be an appropriate approach. Indeed, utilising the results of this observational study as a basis for fatigue-management intervention development, identifying the presence of daytime sleepiness can guide diagnostic evaluations with respect to comorbid sleep disorders, allowing potential treatment by effective countermeasures for sleepiness (Popp et al., 2017).

4.2.6 *Brief Illness Perceptions Questionnaire (BIPQ)*

The BIPQ (Broadbent et al., 2006) uses a single-item scale approach to assess illness perceptions. It is a shorter version of the original Illness Perception Questionnaire (Weinman et al., 1996) which is utilised to assess five dimensions within a cognitive representation of illness. The brief version consists of seven items: five of the items assess cognitive illness representations (consequences, timeline, personal control, treatment control and identity) and two of them assess emotional representation (concern and emotions). Each item (*e.g.* "How concerned are you about your fatigue?") is rated using a response scale of 0 to 10; in which higher scores represent more threatening views of fatigue. The total scoring ranges from 0 to 70, with a higher score reflecting

a more threatening view of illness. The psychometric properties of this measure have been assessed using samples from several illness groups in 26 languages from 36 countries. Findings show that the BIPQ good concurrent and predictive validity (Broadbent et al., 2015). The BIPQ has been utilised with IBD cohorts to assess the relationship between IBD illness perceptions, health status and disability (van der Have et al., 2015); however there are no normative data for patients with IBD. As suggested by the authors (Broadbent et al., 2006), to make the questionnaire more relevant to the studied patient group, the more general word ‘illnesses’ was replaced by the word ‘fatigue’.

4.2.7 Cognitive Behavioural Response to Symptoms Questionnaire (CBSQ)

The CBSQ has been used to measure patients’ cognitive and behavioural responses to their symptoms (fatigue) in patients different conditions including, MS (Casey et al., 2016, Skerrett and Moss-Morris, 2006, Knoop et al., 2012), IBS (Chilcot and Moss-Morris, 2013), renal disease (Chilcot et al., 2016) and chronic fatigue syndrome (Wearden and Emsley, 2013). The questionnaire consists of 42 items in the form of statements. It includes five cognitive subscales; fear avoidance, embarrassment avoidance, catastrophising about symptoms, beliefs that symptoms are a signal damage to the body (damage beliefs), and symptom focus. There are also two behavioural subscales, resting and avoidance of activity and all-or-nothing behaviour. All items are scored on a five-point frequency scale ranging from never (0) to all the time (4). Item scores are added from each subscale to obtain a total score. The questionnaire has shown acceptable internal reliability in a previous study (Skerrett and Moss-Morris, 2006).

4.2.8 Cohen Perceived Stress Scale (CPSS)

The CPSS (Cohen et al., 1983) was developed to examine the role of stress in disease (in the last month). It assesses perceived stressful situations and stress reactions on a cognitive and emotional level. The questionnaire contains 14 items and each item is scored from 0 to 4; a global score is then computed ranging from 0 to 56, with higher scores indicating greater perceived stress. A cut-off of >21 for high short-term perceived stress has been utilised with patients with CD (Langhorst et al., 2013). Rather than rating events or situations, it assesses how the individual globally perceives stress, thereby encompassing the general perceived predictability, controllability, and manageability of challenging situations, their personal impact and meaning, and each individual’s perceived capacity to cope with the challenges effectively (Targownik et al., 2015). This measure of perceived stress has shown greater predictive utility in models of health-care outcomes than have measures assessing the occurrence of recent negative life events or ratings of the perceived impact of these specific negative events (Vermeire et al., 2010).

4.2.9 *Inflammatory Bowel Disease Distress Scale (IBD-D)*

The IBD-D (Woodward et al., 2016) is a newly developed scale designed to identify and measure distress related to IBD. It assesses how IBD has made patients feel during the last 3 months. Patients are provided with a list of issues and have to rate whether these cause them distress on a 6-point Likert scale, ranging from 'Mildly distressing' to 'Highly distressing'. At the time of use for the PhD cross-sectional study, the measure was in the process of psychometric validation. The scale has now been validated and the publication is in press. It has content and construct validity, as the items were derived from interviews with people with IBD and by a steering group that included service users. Issues of psychological morbidity (anxiety and depression), emotional coping and psychosocial stress, do not appear to reflect the whole experience of people with IBD. Indeed, people may feel distressed about their condition without being depressed or anxious, feeling stressed or feeling like they are coping poorly (Woodward et al., 2016). Whilst disease-related distress is a widely used patient reported outcome measure in diabetes (Sturt et al., 2015, Dennick et al., 2017), the association between disease-related distress and IBD has only been shown utilising general distress indicators such as the Global Severity Index from the Brief Symptom Inventory. Despite still being in the process of validation at the time of use, the IBD-D was included in order to identify the association between IBD-fatigue and distressing factors which are specific to patients with IBD.

Chapter 5

5 Paper 3 - Cognitive behavioural therapy for the management of inflammatory bowel disease-fatigue with a nested qualitative element: study protocol for a randomised controlled trial

This chapter includes the published protocol of the PhD intervention (Artom et al., 2017), published as Paper 3 of this PhD thesis. Before presenting the published paper, this chapter describes the process of intervention development. This includes a description of the process of initial adaptation of the CBT manual for MS-fatigue (van Kessel et al., 2008) to a manual for IBD-fatigue and the Patient and Public Involvement activity with patients and HCPs. The steps involved in improving the readability of the text, making the graphic design of manual more acceptable to patients and obtaining input from the therapists are presented. A copy of the intervention manual is presented in Appendix XI.

After the published paper, this chapter presents a justification for the choice of a telephone intervention modality, and an additional description and justification for the methods chosen for the intervention protocol. This includes a further justification for the choice of feasibility, acceptability and initial estimates of efficacy outcomes of the pilot intervention study. Eligible patients were provided with a Patient Information Sheet (Appendix XII) explaining the nature and the aims of the study. Patients had the opportunity to fully consider their participation in the study for at least 48 hours. A signed Patient Consent Form (Appendix XIII) was returned with the baseline questionnaires by post. The study was granted ethical approval by the United Kingdom National Research Ethics Service - North West - Liverpool Central Committee (16/NW/0791, Appendix XIV). At the time of ethical approval, permission was granted also for questionnaire data collection at 6 and 12-months' post-randomisation follow-up points. However, due to the limited time-frame of this PhD project, only the baseline and 3-months post-randomisation results of the pilot intervention study were analysed and reported in this thesis. A statement of the contribution of the PhD student to this paper appears at the end of the paper on Page 123. Amendments to the published paper suggested by the PhD examiners following the oral examination are presented in Appendix XIX.

5.1 Fatigue-related commonalities between IBD and MS

Quantitative (Jones et al., 2009, Kwakkenbos et al., 2015) and qualitative studies (Czuber-Dochan et al., 2013b), and systematic reviews (Czuber-Dochan et al., 2013a, Artom et al., 2016a) have shown similarities in the perceived experience of fatigue between IBD and other disease groups.

Across long-term conditions patients have described losing control of their body because of the intensity of the fatigue experience and/or the unpredictability of fatigue. Fatigue also made it difficult to plan activities ahead of time with a consequent reduction in participation to social events. Additionally, invisibility of fatigue and difficulty in expressing its severity and impact led to a perception of lack of understanding from others (Whitehead et al., 2016). Similarities across conditions are also reported in patients' experiences of managing their fatigue. Most patients sought relief from fatigue by sleeping or resting. Likewise, they adjusted their activity levels to fit with their reduced capacity (Eilersten et al., 2015).

Specifically, parallels exist between descriptions of IBD-fatigue and fatigue in MS, with both patient groups describing fatigue as lack or loss of energy and not being able to stay awake (Czuber-Dochan et al., 2013b). In a study comparing MS and ulcerative colitis (Bol et al., 2010), no significant differences were found in independent contributors to physical and mental fatigue between the two patient groups. Both MS and IBD are autoimmune, inflammatory, chronic and intermittent diseases. Furthermore, both MS and IBD can have a significant negative impact on physical, mental and social well-being (Klevan et al., 2014, Lönnfors et al., 2014). It is therefore possible that similar immune system dysregulation processes could lead to fatigue in the two conditions. Based on the similarities in the experiences of fatigue and the likely similar mechanisms causing fatigue between MS and IBD, it was seen reasonable to adapt an existing successful MS-fatigue intervention rather than starting from scratch with intervention development.

5.2 Adaptation of MS fatigue management intervention manual

Permission was granted by Van Kessel and colleagues to utilise and modify their intervention manual for the management of MS-fatigue. A copy of the manual was obtained in digital format in June 2016. The manual entitled 'Managing your multiple sclerosis fatigue: a cognitive behavioural therapy manual' was composed of 100 pages in Microsoft Word in plain black and white text. The manual was structured with: an introduction section, an instruction section and eight intervention sessions. The intervention manual was read in full by the PhD student (MA) and the PhD supervisors (CN, JS, WCD). A series of preliminary steps were then undertaken by the PhD student to adapt the MS-fatigue manual to a manual for IBD-fatigue prior to the Patient and Public Involvement activities. First, the title of the intervention was changed. The acronym 'MODIFY Fatigue' was drawn from the full name of the manual 'Managing your Inflammatory Bowel Disease Fatigue' to indicate the proposed intention of the intervention to modify the severity and impact of fatigue on patients' daily activities. Second, the term 'multiple-sclerosis' was substituted with 'inflammatory bowel disease' throughout the manual. Third, all sections of the manual containing disease-specific information were either removed, modified or signposted

to be further addressed by HCPs during the stakeholder engagement activity. Modifications to sections of the manual relating specifically to IBD or IBD-fatigue were conducted based on evidence from previous quantitative, systematic review and qualitative studies conducted by Czuber-Dochan and colleagues (2013a,b); clinical IBD guidelines (*e.g.* European Crohn's and Colitis Organisation, British Gastroenterology Society) and information provided by the national charity, Crohn's and Colitis UK. Sections of the manual containing more specialised medical information, were deferred to the specialised knowledge of HCPs working with IBD. Fourth, the title page and instructions section of the manual (Using the Manual), was modified to reflect the MODIFY Fatigue intervention protocol. The process of adaptation of the MS-fatigue intervention to the IBD-fatigue intervention is similar to the one conducted by others in adapting this MS-fatigue intervention (van Kessel et al., 2008) to cancer (Corbett et al., 2016) and renal fatigue (Picariello et al., 2018).

5.3 Stakeholder HCPs engagement activity

A stakeholder engagement activity was conducted with HCP working with patients with IBD. One IBD-nurse specialist and one gastroenterologist were asked to review the content of the entire manual, particularly focusing on sections relating to disease-specific information (*e.g.* IBD symptoms, medications, aetiology). When information was considered incorrect or insufficient, HCPs were encouraged to add further detail based on their medical knowledge and experience working with patients with IBD. All differences of opinion or queries were resolved through discussion with the supervisory team. The final version of the manual to be presented to the patients, was approved by both HCPs.

5.4 Patient and Public Involvement activity

A Patient and Public Involvement activity with patients with IBD was then undertaken to achieve face and content validity of the intervention. The Patient and Public Involvement activity was conducted in order to tailor the intervention to IBD-patients' needs and determine which elements were relevant, acceptable and useful when adapting an intervention for the management of fatigue to patients with IBD. Next, nine IBD patients were invited to take part in a Patient and Public Involvement activity. Invited patients were either known to the supervisory team for having taken part in previous Patient and Public Involvement activities or were referred by Crohn's and Colitis UK charity. Of these, 4 patients accepted to be involved and were sent a paper copy of the manual via post together with instructions on how to complete the activity and a structured feedback form (Appendix XV) to complete. In the instructions, the aims of the Patient and Public Involvement activity and of the study were explained. They were then asked to read the manual carefully, answer the questions on the feedback form and make annotations on the manual as they read it.

Completed feedback forms together with the annotated manuals were returned via mail prepaid return envelopes.

The feedback form (Appendix XV) was 7 pages long and contained 30 open and Likert scale questions regarding: overall impressions of the manual, language and comprehension, format and organisation, usefulness of the manual and feasibility of the intervention tasks described in the manual. All participants commented on the size of the CBT manual, implying that receiving the manual as a single book may be overwhelming for patients with fatigue. A decision was therefore made to present the manual in a ring binder, with separate colours for each session. The ring binder allowed patients to move pages according to their preference. The separate colours were chosen to encourage patients to undertake each session individually instead of reading the manual as a whole. The participants found the language clear and understandable, however further readability assessment tests were conducted so the manual complied with the plain English guidelines (Plain English Campaign 2017). The format and organisation of the manual were not rated very highly. In particular, the need for more colour, pictures and bullet points was highlighted. The manual was also considered to be too text heavy and dense with information per page. In light of these comments on the formatting of the manual, a decision was made to engage a graphic designer to make the manual more user friendly.

The content of the manual was perceived as useful and relevant in helping people with IBD to manage their fatigue. Indeed, participants reported acquiring new knowledge in relation to their fatigue as a result of reading the manual. In line with the therapeutic objectives of the intervention, information regarding monitoring and planning of activity, negative cognitive-behavioural responses to fatigue and sleep were considered particularly relevant to participants' experience of fatigue. Having more information about these aspects of fatigue made them more aware of their own cognitive-behavioural patterns in relation to fatigue and ways in which they could be modified. These comments were consistent with the notion that cognitive-behavioural mechanisms related to fatigue may be comparable across conditions and that an adapted version of a manual for MS-fatigue could be applicable to patients with IBD-fatigue. However, participants highlighted the need for more IBD-specific examples of maladaptive cognitions and behaviours, to make the content more tailored to the IBD population. Indeed, tailoring the content of the intervention can enhance the relevance of the information presented and lead to greater desired changes in response to the communications (Hawkins et al., 2008). Consequently, whilst keeping the therapeutic content drawn from the CBT manual for MS-fatigue (van Kessel et al., 2008), more examples and quotes specific to people with IBD from qualitative studies conducted by Czuber-Dochan and colleagues (2013b) were incorporated in the IBD-fatigue manual. Lastly,

the intervention tasks were perceived to be feasible to complete with adequate organisation and motivation levels.

5.5 Readability assessment

The use of jargon-free language is recommended for all health-related content (Stableford and Mettger, 2007). Nonetheless, evidence shows that 43% of English population of working-age find health material containing text only, too complex to be able to understand and use (Rowlands et al., 2015). It is thus important to consider readability of the content when designing interventions, as the efficacy of interventions can be limited if materials cannot be read or understood by patients (Protheroe et al., 2017). The Flesch-Kincaid system (Farr et al., 1951) is the most widely used computerised method for assessing readability statistics for text (Paasche-Orlow et al., 2003). It is composed of the Flesch Reading Ease test and the Flesch-Kincaid Grade Level test. The Flesch Reading Ease test rates text on a 100-point scale. The higher the score, the easier it is to understand the document. The score is computed using the average number of syllables per word and words per sentence. Syllables-per-word is a measure of word difficulty. Words-per-sentence is an indicator of syntactic complexity. The Flesch-Kincaid Grade Level test rates text on a United States school grade level. The Flesch-Kincaid score has the advantage of measuring the readability of a document based on the minimum education level required for a reader to understand it. The Flesch-Kincaid system was chosen to test the readability of the manual for its excellent reproducibility and high correlation to other readability scales (Paasche-Orlow et al., 2003).

After incorporating the feedback from the Patient and Public Involvement activity, the Flesch Reading Ease test and Flesch-Kincaid Grade Level tests were run on the IBD-fatigue intervention manual utilising Microsoft Word. In order to have representative data for the whole manual, three sections from different sessions of the manual were selected. Flesch Reading Ease test scores were 37%, 64% and 61% for the three sections tested. Flesch-Kincaid Grade Level test scores were grade 12, grade 9 and grade 9. Based on these scores, the need to improve the readability of the intervention manual was recognised. Following the plain English guidelines (Plain English Campaign 2017), the aim was to enhance the Flesch Reading Ease scores to 70% and reduce the Flesch-Kincaid Grade Level scores to grade 8. This was done by changing passive verbs to active verbs, shortening or breaking-up long sentences and paragraphs, using lists when appropriate, using pronouns such as ‘you’ and ‘we’ and reducing the density of complex words. This process was conducted in two stages: the PhD student initially enhanced the readability up to 60%, throughout the manual, and subsequently, a professional medical writer was employed to complete the process and bring the manual to the required readability level. All changes were made through track changes in Microsoft Word in order to allow for full transparency of the

process and facilitate a consensual agreement of the final text. All disagreements or queries were resolved through discussion. The final version of the manual (Appendix XI) was approved by all members of the supervisory team.

5.6 Graphic design

A graphic designer, working internally at King's College London, was engaged to make the design more user friendly. All changes reflected feedback from the Patient and Public Involvement activity and were made in accordance with the supervisory team's requests. The section headings were inserted to keep formatting consistent across sections and high contrast colour text was added to improve flow and readability. Aside from colour, font was kept as simple as possible to encourage easy reading. A picture of the windy road towards recovery was inserted on the front page of the manual to make it more visually appealing. In order to streamline access to the homework sheets, all homework tasks were moved to the end of the intervention manual as a separate homework booklet. Aside from homework sheets for each section, spare homework sheets were provided for patients who may have wished to complete additional tasks during or after the completion of the intervention. The manual was presented in a ring binder so as to enhance flexibility of use of the manual and encourage participants to move the order of its content according to their preference. Each session of the intervention was colour coded to facilitate communication with the therapist with reference to specific sessions. The colour of each session was also signposted in the contents page of the manual. At the end of the design editing process the manual was reviewed and approved by the supervisory team.

5.7 Therapists' input

Once the content, language and formatting of the manual were approved by the research team, the final version of the manual was submitted for approval by the two therapists who would deliver the intervention. The therapists were asked to comment on the ease of use of the manual to deliver the therapy and to share their professional opinion on the cognitive-behavioural therapeutic aspects of the manual. Both therapists provided positive comments regarding the ease of use and therapeutic content of the manual. Clinical experience, grounded in daily trial-and-error practice, contributes to making sense of 'what works for whom' (Roth and Fonagy, 2013) and therapists' accumulated practice-based knowledge is considered a rich source of evidence regarding effective interventions (Westen et al., 2004). As such, the therapists' positive comments were valuable in confirming the intervention manual. Only minor modifications to the language were suggested and inputted. The final version of the manual was provided to participants randomised to Group 1 of the intervention.

5.8 Control intervention

Participants who were randomised to the control group received the Crohn's and Colitis UK 'Fatigue in IBD' Information Sheet (Appendix XVI) to be used without therapist help. The Fatigue in IBD Information Sheet was developed by CCUK together with the two members of the supervisory team (CN, WCD) to explain what fatigue is, what may cause it and possible ways of reducing. The Information Sheet was chosen as the control intervention as it provided valid and empirically tested information about fatigue to patients, without incorporating the principles of CBT. Studies testing CBT interventions for fatigue in other conditions such as cancer in the UK, have also utilised information booklets developed by their national charities as their control conditions (Corbett et al., 2016).

STUDY PROTOCOL

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Cognitive behavioural therapy for the management of inflammatory bowel disease-fatigue with a nested qualitative element: study protocol for a randomised controlled trial

Micol Artom^{*} , Wladyslawa Czuber-Dochan, Jackie Sturt and Christine Norton

Abstract

Background: Fatigue is one of the most prevalent and burdensome symptoms for patients with inflammatory bowel disease (IBD). Although fatigue increases during periods of inflammation, for some patients it persists when disease is in remission. Compared to other long-term conditions where fatigue has been extensively researched, optimal management of fatigue in patients with IBD is unknown and fatigue has rarely been the primary outcome in intervention studies. To date, interventions for the management of IBD-fatigue are sparse, have short-term effects and have not been implemented within the existing health system. There is a need to integrate current best evidence across different conditions, patient experience and clinical expertise in order to develop interventions for IBD-fatigue management that are feasible and effective. Modifying an existing intervention for patients with multiple sclerosis, this study aims to assess the feasibility and initial estimates of efficacy of a cognitive behavioural therapy (CBT) intervention for the management of fatigue in patients with IBD.

Methods: The study will be a two-arm pilot randomised controlled trial. Patients will be recruited from one outpatient IBD clinic and randomised individually to either: Group 1 (CBT manual for the management of fatigue, one 60-min session and seven 30-min telephone/Skype sessions with a therapist over an eight-week period); or Group 2 (fatigue information sheet to use without therapist help). Self-reported IBD-fatigue (Inflammatory Bowel Disease-Fatigue Scale) and IBD-quality of life (United Kingdom Inflammatory Bowel Disease Questionnaire) and self-reported disease activity will be collected at baseline, three, six and 12 months post randomisation. Illness perceptions, daytime sleepiness, anxiety and depression explanatory variables will be collected only at three months post randomisation. Clinical and sociodemographic data will be retrieved from the patients' medical notes. A nested qualitative study will evaluate patient and therapist experience, and healthcare professionals' perceptions of the intervention.

Discussion: The study will provide evidence of the feasibility and initial estimates of efficacy of a CBT intervention for the management of fatigue in patients with IBD. Quantitative and qualitative findings from the study will contribute to the development and implementation of a large-scale randomised controlled trial assessing the efficacy of CBT interventions for IBD-fatigue.

Trial registration: ISRCTN Registry, ISRCTN17917944. Registered on 2 September 2016.

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Background

Inflammatory bowel disease (IBD) mainly encompasses two related but distinct conditions of the gastrointestinal tract: ulcerative colitis (UC) and Crohn's disease (CD). UC is characterised by diffuse mucosal inflammation limited to the rectum and colon. CD is characterised by patchy, transmural inflammation, affecting any part of the gastrointestinal tract from the mouth to the anus [1–3]. IBD is a lifelong condition, which frequently presents in adolescence or young adulthood and follows an unpredictable relapsing and remitting course. The prevalence of IBD in the United Kingdom (UK) is about 300,000 with CD and UC affecting 5–10 and 10–20 new patients, respectively, per 100,000 people per year [4].

Patients with IBD are affected by a number of symptoms, undergo lifelong pharmacological treatment and have an increased risk of malignancy [5, 6]. Due to the severity of IBD, psychological distress is also common [7], with prevalence of symptoms of depression and anxiety around 22% and 35%, respectively [8]. As IBD has an early life onset, a chronic nature and does not generally shorten lifespan, addressing how patients deal with their disease is an important aspect of care [9]. The current standard care in IBD treatment is aimed at managing the inflammatory response during flare episodes and maintaining remission, with an emphasis on adhering to a regular medication regime [10]. However, manifestations of IBD cannot be fully accounted for by pathophysiology and the simple targeting of inflammation does not necessarily reduce the symptoms affecting patients the most [11–13]. In line with the international expert consensus of the recent Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative [14] on treatment targets for IBD, it is therefore important to shift from management of IBD aimed solely at achieving endoscopic remission to also evaluating patient reported outcomes (PROs) with the ultimate goal of improving patients' quality of life (QoL) [15].

Fatigue is a common and predominant concern for patients with IBD, experienced by 44–86% of patients with active disease and 22–41% of patients in remission [16]. Fatigue is a complex, multifactorial and multidimensional phenomenon, which has been described as a 'persistent overwhelming sense of tiredness, weakness, or exhaustion' [17], that can be mental, physical or both [18]. Unlike everyday tiredness, fatigue is often unrelieved by sleep or rest [19], can have a substantial negative impact on patients' QoL [20–23] and it may limit patients in their everyday lives [24]. Although fatigue understandably increases during periods of inflammation, for some patients it persists when disease is in clinical and endoscopic remission [25].

Despite the pervasiveness of fatigue as a chief complaint in IBD patients [23], it is only identified and treated in a

relatively small proportion of those affected [26]. The causes of fatigue in IBD are not well understood by either patients [27] or healthcare professionals (HCPs) [28]. Disease activity [22, 29–31], anaemia [32–34] and inflammation [32] have been found to be predictive of fatigue, yet there is a considerable number of IBD patients with no apparent physiological underpinnings for their fatigue [35]. Apart from a consistent relationship with disease activity, IBD-fatigue has been linked to psychosocial factors such as low mood [31, 36, 37] and sleep problems [29, 31, 37, 38]. However, most previous research has focused on the relationship between fatigue and clinical variables. The ways in which clinical variables and potentially modifiable factors interact with each other in fatigue has rarely been explored [39].

The complex aetiology of fatigue [16], its subjective nature [40] and the lack of objective 'gold standard' to measure fatigue [41], also add to the challenge of developing suitable and effective management methods. Optimal management of fatigue in patients with IBD is unknown and fatigue has rarely been the primary outcome in intervention studies [42–45]. Pharmacological trials utilising biologic therapy [46–48], thiamine [43] or ferumoxitol [49] have shown potential benefits for fatigue. However, these are contrasted by findings in observational studies showing higher fatigue in patients taking biologic therapy [23, 30, 31] and it is unclear whether these effects are due to a reduction in inflammation or to a direct influence on fatigue-signalling pathways [50]. Despite the known importance of physical activity in IBD-fatigue [31, 51], the only trial [45] examining the effect of advice to increase physical activity provided inconclusive results. A few psychosocial interventions, such as problem-solving, solution focused therapy (SFT) [42, 44] and stress management [52], have shown promising effects which declined over time and studies included only a small number of participants.

Stress management [52] has been compared with conventional medical treatment in 45 patients with CD. Self-directed stress management significantly reduced tiredness post-treatment, at six-month and 12-month follow-up. However, fatigue was measured with a symptom diary rating devised by the authors and not with a validated fatigue scale for the assessment of fatigue in long-term conditions [41]. Moreover, fatigue was not the primary outcome of the intervention, making the mechanisms of change difficult to assess. The efficacy of SFT on fatigue and QoL was evaluated in 98 patients with quiescent IBD [44]. After the intervention and at three-month and six-month follow-up, the SFT group showed a significantly greater reduction in fatigue and improvement of QoL comparable to the care as usual group. Yet, the effect was not maintained at nine months post intervention. It is therefore important to design interventions with

longer-term effect of reducing fatigue (with follow-up assessments of a minimum of 12 months), in order to determine whether positive effects of interventions can be sustained over long periods of time, and if not, establish the reasons for loss of response over time [53].

Compared to IBD, where fatigue has not been well described, understood or managed [16], in other long-term conditions fatigue has been extensively researched. Drawing from evidence on fatigue in other chronic conditions with relapsing and remitting trajectory, such as multiple sclerosis (MS) and rheumatoid arthritis (RA), can help to identify the mechanism in which psychosocial and clinical factors interact with each other and contribute to higher levels of fatigue, and identify types of interventions for fatigue management in IBD patients. A few fatigue treatment protocols based on cognitive-behavioural models [54–56], employed in large-scale randomised controlled trials (RCTs) in inflammatory conditions (e.g. MS, RA) have found promising results in fatigue reduction [57–59]. Although varying across conditions and symptoms, cognitive-behavioural models are based on the premise that symptoms are maintained by maladaptive cognitive and behavioural factors [60]. Initially, primary disease factors, such as inflammation, may trigger symptoms of fatigue. The ways in which people react cognitively, emotionally and behaviourally to their fatigue may perpetuate or worsen the symptoms [54]. Consequently, altering cognitions, emotions and behavioural responses in relation to fatigue through cognitive-behavioural therapy (CBT) may improve clinical and psychosocial outcomes [61, 62].

Van Kessel et al. [57] assessed the efficacy of delivering CBT or relaxation training (RT) to 72 patients with MS and found that the CBT group reported significantly greater reductions in fatigue nine months post intervention compared to the RT group. Thomas et al. [62–64] compared six weekly sessions of group-based CBT with current local practice in 164 patients with MS and found statistically significant differences in fatigue severity in favour of the intervention group four months and one year post intervention. Similarly, in a two-arm, parallel RCT in adults with RA, Hewlett et al. [58] compared six weekly sessions and a consolidation session of group CBT with self-management information in a 1-h didactic group session. At 18 weeks from the intervention start, CBT participants reported better scores than control participants for fatigue impact and perceived fatigue severity.

For people with IBD, CBT has been utilised for a variety of outcomes, including relapse reduction [65] and perceived stress [66]. Six systematic reviews have collectively appraised studies of psychological treatment for IBD [67–72] with encouraging results. In the most recent systematic review and meta-analysis [72] of RCTs comparing psychological therapy with a control intervention or a

control treatment (14 studies), a significant difference in depression scores and quality of life with psychological therapy was observed at the end of therapy in patients with quiescent disease. However, beneficial effects were lost at the final point of follow-up. When assessing the effect of individual physiological therapies on quality of life, only CBT had any significant beneficial effect. In a systematic review of 17 studies, Goodhand et al. [68] concluded that CBT was effective for mood disorders and improved QoL in patients with IBD. McCombie et al. [71] and Knowles et al. [70] evaluated studies of the main types of psychological treatment for IBD and found that CBT and its variants most commonly contributed to positive outcomes as compared to other psychotherapies (i.e. psychoeducation and problem-solving therapy). CBT consistently resulted in improved psychological distress, but with modest effects in gastrointestinal symptoms these were not sustained over time. However, these findings have to be interpreted in light of limitations, including: time and travel burden for patients attending face-to-face sessions; and high attrition rates and low compliance issues for online interventions [73, 74].

There is a need to integrate current best evidence across different conditions, patient experience and clinical expertise in order to develop interventions for IBD-fatigue management that are feasible and effective [75]. Balancing the insights from research and practice can maximise the likelihood of interventions being feasible and acceptable, and of treatment addressing important issues to patients while overcoming previously identified limitations [76].

There is evidence from RCT interventions in other long-term conditions [57–59] to suggest that modifying maladaptive cognitions and behaviours through CBT could be a viable option for the management of fatigue. Drawing from interventions in other conditions can enhance the process of development of new evidence-based management strategies in IBD without ‘reinventing the wheel’ [77]. Previous quantitative [78, 79] and qualitative studies [80] and systematic reviews [16, 39] showed similarities between the perceived experience of fatigue between different disease groups. Across conditions, fatigue is closely related to relapse and more active disease [81, 82] and similar physical and psychosocial factors appear to be causing and exacerbating fatigue [80]. Additionally, the findings from our recent study [83] indicate that the ways patients perceive, interpret and react to fatigue symptoms in IBD is largely comparable to patients with MS specifically [84]. Patients who have more negative perceptions of fatigue, higher levels of all-or-nothing and avoidance behaviours have significantly greater fatigue scores compared to those with less negative cognitions and behaviours in relation to their fatigue.

Based on these premises, the CBT intervention developed by Van Kessel and colleagues [57] for MS was chosen as the basis of our intervention study for IBD patients.

Iterative work with both patients and HCPs working with patients with IBD was then conducted in order to tailor the intervention to IBD patients' needs following the guidelines on Patient and Public Involvement (PPI) involvement in healthcare [85, 86]. An initial trial has shown promising results with patients with MS [57], has a strong theoretical grounding in a CBT model [87] and has incorporated a valuable and in-depth mediation analysis of processes of change after the trial [88]. The intervention involved eight weekly sessions of 50 min and covered: an introduction to the CBT model of fatigue; activity scheduling; changing unhelpful cognitions surrounding MS and fatigue; sleep hygiene and restoring sleep-wake cycles; managing negative emotions; and the role of social support. In MS, calculated effect sizes for fatigue from baseline to the end of treatment were 3.03 for the CBT group and 1.83 for the RT group, with clinically significant improvements in fatigue. Furthermore, in our study [83], negative perceptions of fatigue and avoidance behaviours were identified in patients with IBD. In MS patients in the trial [88] these same perceptions of fatigue and avoidance behaviours improved significantly more in the CBT than in the RT group. Changing negative perceptions of fatigue mediated the decrease in severity of fatigue [88]. Content of the intervention is described in more detail in Van Kessel et al. [57].

As a result of the challenges inherent in evaluating complex interventions such as CBT, the UK Medical Research Council (MRC) Framework for the development of complex intervention [89] recommends a stepwise approach, with an early piloting phase prior to the design of a large-scale trial. Pilot studies resemble the main study in many respects [90], they are a smaller version of the main study that test whether its components can all work together [91]. They are a requisite initial step in exploring a novel intervention [92] and resemble the main study in many respects, including an initial assessment of the primary outcome [93]. The pilot phase hence ensures that money is not wasted on an expensive trial which produces a null result due to problems with recruitment, retention or delivery of the intervention [94] and that end results are more applicable to real-world settings. It was therefore decided to conduct a pilot study prior to a definitive full-scale effectiveness RCT.

The MRC guidance for process evaluation of complex interventions [95, 96] advocates the potential value of the qualitative research in health interventions. This is part of the growing call to move away from the inappropriate use of pilot trials as hypothesis testing to a greater emphasis on their descriptive, feasibility potential [97]. RCTs are considered the 'gold standard' for providing evidence in decision-making in evidence-based practice [98], yet they have been criticised for not providing sufficient evidence that is useful in practice [99]. After the trial, qualitative approaches can help to explore reasons for the findings,

examine the appropriateness of the underlying theory and steer researchers towards interventions more likely to be effective in the future [100]. Furthermore, qualitative process evaluation supports understanding and explanation of the processes involved during the implementation of an intervention and its potential integration in everyday practice [101]. To date, only an estimated 3–8% of trials have incorporated qualitative research components [102]. The current pilot trial will hence include a nested qualitative component, with interviews with the IBD patients, the therapist/s delivering the intervention and HCPs working with patients with IBD. The nested qualitative component will strengthen the findings by evaluating perceptions of the current pilot intervention and ultimately enhance the acceptability of the intervention in a large-scale trial.

Research questions: What is the feasibility of a CBT intervention for the management of fatigue in patients with IBD? What are the initial estimates of efficacy of an intervention for the management of fatigue in patients with IBD?

Methods and design

This study will assess the feasibility and initial estimates of efficacy of a CBT intervention for the management of fatigue in patients with IBD. The pilot intervention will have the objectives to:

- Assess the feasibility of recruiting eligible patients;
- Assess the willingness of participants to be randomised;
- Evaluate the compliance rates to the intervention (Therapist Sessions and Homework Sheets);
- Assess withdrawal and dropout rates during the treatment phase;
- Assess the completion rates of the outcome measures post intervention and at follow-up times;
- Determine the adequate sample size for definitive full-scale effectiveness RCT;
- Obtain initial estimates of efficacy on fatigue and QoL in the CBT intervention group compared to the fatigue Information Sheet group;
- Obtain detailed qualitative feedback from patients, the therapist/s delivering the intervention and HCPs working with patients with IBD on their experience and views of the intervention and areas for improvement in future fatigue interventions.

The pilot trial will not attempt to provide evidence of clinical effectiveness for the CBT intervention in people with IBD. This is in accordance with the recommendations from the National Institute of Healthcare Research (NIHR) guidelines and the Consolidated Standards of

Reporting Trials (CONSORT) for the development of pilot studies [91, 103].

Study design

The study will be a two-arm pilot RCT. Patients will be recruited from the outpatient IBD clinic at a single specialist hospital site and randomised individually, using a 1:1 ratio computerised algorithm. A nested qualitative study will evaluate patient and therapist experience, and HCPs perceptions of the intervention. The study will have a total duration of 22 months with two phases.

Phase 1: the pilot randomised controlled trial ($n = 40$)

Recruitment

A member of the direct care team at the recruitment site will look through electronic and paper medical records, reviewing the inclusion/exclusion criteria, and identify potentially eligible patients attending the IBD outpatient clinic that day. Consecutive potentially eligible patients attending outpatient IBD clinics from January 2017 to June 2017 will be included in the recruitment process. At the end of their appointment a direct member of their care team will ask patients if they would be happy to be approached by a researcher to take part in a research study. If the patient is interested, they will then be directed to the research room. A member of the research team will hand the patients a Patient Information Sheet (PIS) and provide them with a full verbal explanation of the RCT. Patients will be given adequate time to fully comprehend the content of the PIS and will be given the opportunity to ask questions about taking part in the study. Those who indicate a potential interest in the RCT will be screened for full eligibility using the Eligibility Screening Form. If ineligible, the patient will be thanked for their interest, will not be enrolled in the study and no personal details will be recorded.

Eligible patients will then be given at least 48 h to consider their participation in the study and discuss the decision with family, friends and their care team. A member of the research team will then contact them by telephone to answer any additional questions, verify their understanding of what is involved and confirm their interest in study participation. If patients agree to take part in the study, they will be asked to sign the *Patient Consent Forms-RCT* and complete the *Baseline Data A* booklet. A format for written questions for this phase has been developed and piloted with our PPI group to ensure acceptability and ease of understanding of questions to be asked. Participants will be asked to return the signed *Patient Consent Forms-RCT* and the completed questionnaires in the pre-paid stamped addressed envelope provided within seven days of receipt. The returned study documents will be checked for completeness, and the patient will then be entered into

the randomisation database for the RCT and told whether they are in Group 1 (CBT manual + therapist support) or Group 2 (Fatigue Information Sheet only). Screening and consenting will continue until the study target sample size ($n = 40$, 20 for each arm) is reached. Hospital consultants will be informed of the patients' participation in the study via an entry made in the patient's notes; with patients' agreement, their General Practitioner (GP) will be informed using *GP Notification Letter*.

Randomisation

Consenting participants will be randomised to CBT manual plus therapist support or Fatigue Information Sheet only using a random number generator with a 1:1 ratio in the Statistical Package for the Social Sciences Version 22. All baseline information will be collected prior to randomisation. Participants will be randomised at the individual level. The randomisation sequence will be generated electronically by an independent statistician prior to the commencement of the study. The statistician will have no patient contact. The trial coordinator (blinded until this point) will access the randomisation database to assign patients to the two groups. Indeed, as this is a small pilot study on a limited budget, there are no resources available to provide a blinded data collector. Owing to the nature of the study the participants, the researchers and the therapist will not be blinded to treatment allocation after randomisation. The trial coordinator will be informed of the outcome of the randomisation procedure in order to identify participants who require telephone support calls during the trial. The researcher conducting the qualitative interviews will also be unblinded to ensure that appropriate questions are asked.

Group 1 (CBT manual + therapist support)

Group 1 participants will receive a CBT manual for the management of fatigue and have one 60-min session and seven 30-min telephone/Skype sessions with a therapist over an eight-week period. All sessions will be over the telephone or Skype according to patient preference. In the Consent Form, patients will be informed that if they choose Skype, information may not be secure and may be transferred to other countries outside the Trust's control. During the intervention, participants will have access to all usual care, including the nurse-led helpline.

CBT manual development

The CBT manual utilised for the intervention will be a modification of the CBT manual for the management of MS fatigue developed by Van Kessel et al. [57]. The manual contains eight sessions. Despite the lack of consensus from systematic reviews on the adequate number of therapy sessions to be used by interventions,

the number of sessions was modelled on the number of sessions utilised in the RCT by Van Kessel et al. [57], where 100% of the subjections in the CBT group completed the eight-session intervention with large effect sizes. The sessions include: IBD fatigue explained; CBT for IBD fatigue; activity scheduling; improving your sleep; understanding IBD symptoms; changing your thinking; managing stress, determining a sense of control and coping with emotions; social support and preparing for the future, and it has an approximate length of 100 pages. One of the authors (Rona Moss-Morris) of the original CBT manual for MS helped in making the initial changes and refinements to the manual incorporating evidence from the first MS trial [57] and its adaptation into an Internet-based CBT self-management programme for fatigue in MS [104].

In order to make the intervention relevant and acceptable to patients with IBD, we have worked with people with IBD-fatigue, consultant gastroenterologists, IBD-nurse specialists, dieticians and psychologists working with people with IBD. Specifically, Session 1 of the intervention manual 'IBD-Fatigue Explained' addresses medical factors causing fatigue which are specific to patients with IBD including inflammation and fatigue and anaemia and fatigue. Furthermore, examples and tasks throughout the intervention manual have been adapted to reflect concerns and issues specific to patients with IBD and not MS. Finally, a medical writer conducted in-depth pre-post readability statistics and performed the required changes to transform the intervention manual into plain English and make the language as clear as possible. Likewise, a graphic designer made the necessary formatting edits to the manual so as to make the design more user-friendly.

Therapists

Patients will have telephone support sessions with one of two qualified CBT therapists who have experience in delivering interventions to patients with long-term conditions. The therapist will receive the manual in advance and have the opportunity to discuss its contents and any questions with the research team. The purpose of the telephone/Skype support calls are to promote engagement with the intervention and to support the patient in collaboratively developing goals to work on using the resources and information available to them in the CBT manual. At the start of each telephone call, the therapist will set an agenda with the participant. The first telephone/Skype support call will be scheduled for when the participant will have completed the first session in the CBT manual.

Group 2 (Fatigue Information Sheet only)

Group 2 participants will receive the Crohn's and Colitis UK (CCUK) 'Fatigue in IBD' Information Sheet to use

without therapist help. CCUK is the UK's leading charity for patients with CD and UC. CCUK provides patients with free online information sheet and guides to help those affected by IBD. As many people with IBD suffer from fatigue, CCUK, together with our research team (CN, WCD), developed an Information Sheet which explains what fatigue is, what may cause it and possible ways of reducing it.

Feasibility and acceptability outcomes

Feasibility of recruiting eligible patients will be evaluated by calculating the proportion of those invited to take part in the intervention that were eligible and then were consented into the trial. The willingness of participants to be randomised will be evaluated by calculating the proportion of those who dropped out of the trial after they have been randomised. Refusal, withdrawal and dropout rates from the study and number of sessions with therapist will be recorded. A post-intervention follow-up questionnaire included in *Outcome Data B* booklet will assess compliance rates to the intervention by asking participants about the number of sessions of the manual they read and time per week spent completing tasks in relation to the intervention. The therapist/s will also record how many sessions the participants have completed. Furthermore, in order to assess compliance to the intervention procedures, if participants are willing to do so, they will be asked to provide the research team with the Homework Sheets completed at the end of each session in the manual. The Homework Sheets will be checked for completion in order to assess compliance with the intervention components.

Initial estimates of efficacy outcomes

Prior to randomisation, eligible participants will complete the study baseline measures which are contained in a single questionnaire booklet. The questionnaire booklet contains 20 printed pages. Preliminary piloting has demonstrated that on average it has taken 10–15 min to complete and our patient representatives have commented that this is not unduly burdensome. Three months post randomisation, the Outcome Questionnaire booklets will be sent by post. Patients who were allocated to the CBT intervention and will be asked further questions about their experience of completing the intervention in order to assess their compliance with the intervention, preferences, acceptability and satisfaction with the intervention. Patients who were allocated to Fatigue Information Sheet only, will be asked about their experience of reading the Fatigue Information Sheet. A postal reminder will be sent to non-responders two and four weeks after the seven-day response period has ended, utilising the Reminder Letter and/or a telephone call. Six and 12 months post randomisation, two more outcome

booklets will be sent respectively, with two postal reminders and/or telephone calls for non-responders after two and four weeks. The booklets will only contain the primary outcome measures IBD-fatigue, QoL UK questionnaire and Disease Activity Indexes (DAIs) specific to the condition.

Twelve months post randomisation

Patients in the Fatigue Information Sheet only group (Group 2) will be offered the CBT manual for managing fatigue in IBD. No therapist support will be offered alongside the manual.

Nested qualitative study ($n = 7$ patients + both therapist/s + approximately three HCPs)

To better understand patient perspectives on the intervention, participants consenting to the RCT might be invited for interview. The interview sub-sample will be purposively selected to include both genders, a range of ages, both IBD diagnoses and those successful and not successful in showing an initial improvement in IBD-fatigue. Purposive sampling has the potential to provide richer, more relevant and diverse data pertinent to the research question [105, 106]. Participants will be asked about the process of recruitment and randomisation, their experience of the intervention itself, their reasons for dropping out or not completing (where appropriate) and areas for improvement in the design of future fatigue interventions for patients with IBD. Patients will receive information about the interviews in the *Patient Information Sheet – RCT and Interviews*. Using the *Patient Consent Form – Interviews*, separate informed consent will be sought for the face-to-face/telephone/Skype, semi-structured interviews with a purposive sample of approximately seven participants (about one-third of the participants in Group 1). Interviews will be conducted by a researcher not involved in the delivery of the intervention and have a duration of 30–60 min.

The nested qualitative study will be conducted after the three-month follow-up quantitative data collection point. The choice of qualitative data collection at three months allows for minimisation of recall bias, patient burden and confounding of participants in the study. The short time period between the intervention and the interviews, ensures that participants will find it easier to recall their experience of the intervention. Indeed, involvement in qualitative data collection as part of an RCT may in some way influence the participant's experience of treatment [107]. However, the gap in time between the interviews and the next follow-up data collection point (six months post randomisation) limits the potential for participants' outcome responses to be influenced by their participation in the interviews. Furthermore, time gap in time between interviews and follow-up questionnaire completion reduces potential patient burden, while still ensuring continuity to the study.

The therapists supporting patients during the intervention will be interviewed to understand their experience of delivering the intervention and to inform future adaptation and delivery of the intervention in clinical practice. HCPs working with patients with patients with IBD at the study site will be interviewed to obtain their views on the intervention and its possible implementation within existing IBD service at a roll out stage. Approximately three HCPs will be interviewed. Informed consent for the interview will be secured using the *Staff Consent Form – Interviews*.

Qualitative analysis

Interviews will be conducted by a researcher who will not be involved in the delivery of the intervention. Interviews will be digitally audio-recorded, anonymised and transcribed verbatim by a professional transcriber. Original audio files and file transcripts will be stored on a secure server at King's College London (KCL) in a password protected file. The transcriber will delete his/her copy of each audio file once transcription is complete. Data will be analysed using thematic analysis [108] and, if appropriate, NVivo11 software for data management. Analysis begins with a coding framework, where key concepts emerging from the transcripts will be mapped. Additional themes emerging are added to the coding framework. The final framework is agreed, then applied to all transcripts. An iterative process will confirm a final coding framework before analysis. Two researchers will code all transcripts independently and then compare and refine resulting codes and themes in discussion. The emergent themes will form the basis of analytical interpretation. Process evaluation data will be analysed separately from outcome data in order to avoid bias in interpretation [109].

Study outcome measures

For feasibility and acceptability outcomes, please refer to Study outcome measures. The primary and secondary outcome measures will be recorded at baseline, three, six and 12 months post randomisation. The primary outcome measure will be utilised to assess initial estimates efficacy of the intervention in the CBT intervention group compared to the Fatigue Information Sheet group. All outcome measures have been validated for self-completion.

Primary outcome measure

IBD-Fatigue Scale (IBD-F)

The IBD-F [110] aims to assess IBD-specific fatigue. The first two sections of the questionnaire, five questions assessing frequency and severity of fatigue and 30 questions rating the experience and impact of fatigue, will be utilised in the study. Higher scores indicate higher fatigue and higher impact of fatigue. Initial validation of the measure suggested that the questionnaire had good

face and content validity, acceptable to excellent test-retest stability and a high degree of internal consistency [110]. Both sections of the IBD-F have been found to be significantly correlated with other widely utilised fatigue scales [22]. The scale was developed by conducting in-depth interviews with participants with IBD, in order to gain insight into their experience and ultimately to represent issues of specific importance to people with IBD fatigue.

Secondary outcome measures

United Kingdom Inflammatory Bowel Disease Questionnaire (UK IBDQ)

The UK IBDQ [111] is the British version of the McMaster IBDQ [112]. It has 32 items, each scored in the range of 1–4, with a summary score between 30 and 120. A low score indicates poor quality of life. Initial findings have supported the reliability, validity, reproducibility and responsiveness of the UK version of the questionnaire. The questionnaire has been found acceptable to patients in the UK. It enhances the precision of some of the questions in the McMaster IBDQ, improves the readability of the questionnaire, removes items that do not provide useful information and simplifies the response categories. The IBDQ was developed with patients with IBD, it therefore reflects the concerns of the patients themselves about the impact of their disease on their life-style and quality of life. The IBDQ is recommended for use in healthcare evaluation to assess the effect of interventions for IBD on QoL [113]. Members of our patient representatives group voted 15:2 in favour of the UK version when compared with the original version, stating 'choices more straightforward'.

Explanatory variables

Disease activity indexes

The Harvey Bradshaw Index (HBI) [114] and the Simple Clinical Colitis Activity Index (SCCAI) [115] will be utilised to measure disease activity for CD and UC patients, respectively. The HBI and SCCAI will be recorded at baseline, three, six and 12 months post randomisation. All other explanatory variables will only be recorded at baseline and three months post randomisation.

Brief Illness Perceptions Questionnaire (BIPQ)

The BIPQ [116] uses a single-item scale approach to assess illness perceptions. It is a shorter version of the original Illness Perception Questionnaire (IPQ) [117] which is utilised to assess five dimensions within a cognitive representation of illness. The brief version consists of nine items: five of the items assess cognitive illness representations (consequences, timeline, personal control, treatment control and identity), two of them assess emotional representation (concern and

emotions) and one item assesses illness comprehensibility. Each item (e.g. 'How concerned are you about your fatigue?') is rated using a response scale of 0–10; in which higher scores represent more threatening views of fatigue. The psychometric properties of this measure have been assessed using samples from several illness groups including IBD [118] and chronic obstructive pulmonary disease [119].

Epworth Sleepiness Scales (ESS)

The ESS [120] is utilised to measure a participant's level of daytime sleepiness. From a clinical point of view this is relevant in that it helps to determine the presence of pathology or simply predict whether sleep onset is likely to occur at inappropriate times [121]. The questionnaire asks participants to rate their chance of falling asleep or dozing on a scale of 0–3 in eight soporific situations, ranging from 'Lying down to rest in the afternoon when circumstances permit' to 'in a car while stopped for a few minutes in traffic'. A total score of 0–24 is determined, with values over 10–11 indicating abnormal or pathological sleepiness. Given its ease of use and cost-effectiveness, the ESS is now one of the most widely used tools for the assessment of sleepiness [122].

Seven-item Generalised Anxiety Disorder Scale (GAD7)

The GAD7 [123] asks participants how often during the last two weeks they have been bothered by each of the seven core symptoms of generalised anxiety disorder. Response options are 'not at all', 'several days', 'more than half the days' and 'nearly every day', scored as 0, 1, 2 and 3, respectively. It has a minimum possible score of 0 and a maximum possible score of 21. The GAD7 has been utilised in studies assessing anxiety severity in diverse conditions, including: patients with eating disorders [124]; multiple sclerosis [125]; and cardiovascular disease [126]. The GAD7 is used as an outcome measure for CBT for anxiety in the UK Improving Access to Psychological Therapies (IAPT) programme [127].

Nine-item Patient Health Questionnaire (PHQ9)

The PHQ9 [128] is based on the diagnostic criteria for major depressive disorders in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). The questionnaire contains nine items, which are scored from 0 (not at all) to 3 (nearly every day), according to the frequency of their experience over the previous two-week period, with a total score in the range of 0–27. The PHQ9 has been found to be a reliable and valid measure [129] and it has been previously validated in gastroenterological patients [130]. The PHQ9 is used as an outcome measure for CBT for depression in the IAPT programme.

Sociodemographic and clinical data

Sociodemographic and clinical data about participants will be collected at baseline in order to better characterise the sample, make the results of the RCT more clinically relevant and appropriately adjusting statistical data analysis. Sociodemographic data collected will include: age; gender; marital status; education status; employment status; and living arrangements. Clinical data will include: IBD diagnosis; co-morbidities; latest measurement of faecal calprotectin concentration; IBD-related medications (name, dose and frequency); length of time since diagnosis (years, months); number of IBD-related surgeries; smoking status (current smoker, ex-smoker, never smoked); exercise status (> or < 30 min of aerobic exercise per week); haemoglobin; ferritin; serum albumin; C-reactive protein (CRP); platelets count; vitamin B12; and folate. These clinical data are routinely collected as part of standard care in patients with IBD at these sites. If the patient does not attend the service at follow-up, it is unknown whether there will be updated clinical data for patients. However, due to potential patient burden and lack of funding, no additional blood tests will be conducted for the patients, even if recent clinical data are not present in the hospital patient records. One value for each clinical marker will be collected if it refers to up to three months prior to or after the completion of the baseline questionnaires.

Participant entry

Patient interviewees will be selected from those recruited for the RCT, who will have been evaluated prior to enrolment. The *Eligibility Screening Form* will be used to conduct pre-registration evaluation of participants for the RCT.

Inclusion criteria

- Patients who are currently experiencing fatigue (self-reported)
- Proof of diagnosis of IBD (record of diagnostic endoscopy in patient clinical notes); patients without this test will not be included
- Aged 18 years and over
- No elevated inflammatory markers or other clinical features of active disease

Exclusion criteria

- Patients without a record of diagnostic endoscopy in their clinical notes
- Elevated inflammatory markers or other clinical features of active disease
- Course of CBT for any reason in the last year

- Currently enrolled in another trial involving a novel pharmacological intervention
- Current or planned pregnancy (pregnant women have been found to be significantly more affected by fatigue and sleep disturbances [131])
- Inability to give informed consent (for example, due to reduced mental capacity)
- Insufficient command of written and spoken English to understand study documents or procedures

Statistics and data analysis

Due to the pilot design of the study a power calculation was not required. Data collected in the pilot study will be used to generate information for sample size calculations for a definitive full-scale effectiveness RCT. Based on similar pilot studies, a sample of 40 patients (20 per arm) was deemed large enough to provide useful information about the aspects that are being assessed for feasibility. It is recognised that the study may not be powered to detect meaningful differences in clinically important endpoints [91].

Patients will be recruited from an IBD outpatient clinic in London, UK, which is representative of the target study population of patients experiencing IBD-fatigue. The sample was based on the same inclusion/exclusion criteria that would be used in a future definitive full-scale effectiveness RCT. At the study site, a total of approximately 100–150 patients attend four IBD outpatient clinics each week. Assuming around 40% recruitment of eligible patients based on our earlier studies recruiting from this population [83], discussions with the clinical team and recruitment rates for intervention for fatigue in MS [57], our target aim of 40 patients should be reached within the six-month baseline data collection period. Taking into account an attrition rate based on prior research [132] of about 20% for each follow-up, we will aim to achieve a minimum sample size of 40 at baseline, in order to suitably assess outcomes at follow-up.

Primary and secondary measures at baseline along with recruitment rates, telephone session attendance, time spent on the intervention, Homework Sheet completion rates and withdrawal from intervention rates will be presented as means and standard deviations for approximately normally distributed continuous variables, medians and interquartile ranges for non-normally distributed variables, frequencies and percentages for categorical variables. Initial estimates of treatment effect on primary and secondary outcomes at the follow-up assessments will use an intention-to-treat (ITT) framework, implemented using a regression model, adjusting for baseline values of the outcome, sociodemographic and clinical outcomes. ITT analysis will compare the primary and secondary outcome measures at three months

between the two randomised groups. ITT analysis will compare only primary outcome measures at six and 12 months between the two randomised groups. Where participants wish to withdraw from the intervention, we will attempt to retain them in the data collection, unless they express a wish to be withdrawn completely.

As this is a pilot study, it is not intended that the study is powered to detect significant differences on the primary or secondary outcome measures. Qualitative data will also be recorded. Protocol conforms to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). See Additional files 1 and 2 at the end of the manuscript for SPIRIT Figure and Checklist.

Discussion

This is the first RCT to utilise CBT for the management of fatigue in patients with IBD. To date, psychosocial interventions utilising problem-solving, solution focused therapy (SFT; 42, 44) and stress management [52] have shown promising effects. However, their effects declined over time [44] and fatigue was not always the primary outcome of the intervention [52]. The study will provide evidence of the feasibility and initial estimates of efficacy of a CBT intervention for the management of fatigue in patients with IBD. Quantitative and qualitative findings from the pilot study will contribute to the development and implementation of a subsequent large-scale RCT assessing the efficacy of CBT interventions for IBD-fatigue.

One of the limitations of the pilot trial is the small number of participants which will impact on the statistical strength of the study. However, the lack of sufficient data about the feasibility and efficacy of CBT for the management of fatigue in this population necessitates the undertaking of an initial pilot upon this issue.

Trial status

Patient recruitment for the study will begin in January 2017 and is expected to continue for six months in total.

Additional files

Additional file 1: SPIRIT Checklist. (DOC 104 kb)

Additional file 2: SPIRIT Figure. (DOC 61 kb)

Abbreviations

CBT: Cognitive behavioural therapy; CD: Crohn's disease; CONSORT: Consolidated Standards of Reporting Trials; CRP: C-reactive protein; CV: Curriculum vitae; DSM: Diagnostic and Statistical Manual; ECCO: European Crohn's & Colitis Organisation; GAD: Generalised Anxiety Disorder; GCP: Good clinical practice; GP: General practitioner; HCP: Healthcare professional; IBD: Inflammatory bowel disease; ITT: Intention to treat; MS: Multiple sclerosis; NHS: National Health Service; NIHR: National Institute of Healthcare Research; NRES: National Research Ethics Service; PPI: Patient public involvement; PRO: Patient reported outcome; RA: Rheumatoid arthritis; RCT: Randomised controlled trial; REC: Research Ethics Committee; RT: Relaxation therapy; SFT: Solution focused therapy; UC: Ulcerative colitis; UK: United Kingdom

Acknowledgements

We acknowledge members of our PPI group who helped us with the study development. We also acknowledge the original authors of the CBT manual for their aid with the intervention development.

Funding

The study was part of a PhD project funded by King's College London.

Availability of data and materials

Not applicable.

Authors' contributions

MA, WCD, CN and JS were responsible for the conception of the study; MA was responsible for the drafting the manuscript. All authors have read and commented on the final version of this article and are responsible for its content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was granted ethical approval by the United Kingdom National Research Ethics Service - North West - Liverpool Central Committee (16/NW/0791). Eligible patients will be provided with a Patient Information Sheet explaining the nature and the aims of the study. Patients will have the opportunity to fully consider their participation in the study. Signed informed consent will be returned with the baseline questionnaires by post. All participants will be allocated a study number to protect their anonymity.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 13 January 2017 Accepted: 3 April 2017
Published online: 11 May 2017

References

- Dias J, Escher J. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis-the Porto criteria. *J Pediatr Gastroenterol Nutr*. 2005;41:1-7.
- Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol Hepatol*. 2005;19(Suppl A):S5A-36.
- Stange E, Travis S, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut*. 2006;55 suppl 1:i1-i15.
- The IBD Standards Group. Standards for the healthcare of people who have inflammatory bowel disease. London: IBD Standards Group; 2013. http://www.ibdstandards.org.uk/attachments/160_IBDstandards.pdf. Accessed 2 May 2017.
- O'Connor M, Bager P, Duncan J, Gaarenstroom J, Younge L, Detre P, et al. N-ECCO Consensus statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis. *J Crohns Colitis*. 2013;7(9):744-64.
- Everts FB, Thijssens N, Stokkers P, Grootenhuys M, Bockting C, Nieuwekeik P, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis*. 2012;6(1):68-76.
- Keeton RL, Mikocka-Walus A, Andrews JM. Concerns and worries in people living with inflammatory bowel disease (IBD): A mixed methods study. *J Psychosom Res*. 2015;78(6):573-8.
- Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory Bowel Disease: A systematic review. *J Psychosom Res*. 2016;87:70-80.
- Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis*. 2009;15(7):1105-18.

10. Kiebles JL, Doerfler B, Keefer L. Preliminary evidence supporting a framework of psychological adjustment to inflammatory bowel disease. *Inflamm Bowel Dis*. 2010;16(10):1685–95.
11. Mikocka-Walus A, Turnbull D, Andrews JM, Moulding N, Wilson I, Holtmann G. Psychogastroenterology: a call for psychological input in Australian gastroenterology clinics. *Intern Med J*. 2009;39(2):127–30.
12. Mikocka-Walus A, Andrews JM, Rampton D, Goodhand J, van der Woude J, Bernstein CN. How can we improve models of care in inflammatory bowel disease? An international survey of IBD health professionals. *J Crohns Colitis*. 2014;8(12):1668–74.
13. Hackett KL, Newton JL, Deane KH, Rapley T, Deary V, Kolehmainen N, et al. Developing a service user informed intervention to improve participation and ability to perform daily activities in primary Sjögren's syndrome: a mixed-methods study protocol. *BMJ Open*. 2014;4(8):e006264.
14. Peyrin-Biroulet L, Sandborn W, Sands B, Reinisch W, Bemelman W, Bryant R, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110(9):1324–38.
15. Willert N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2014;12(8):1246–56, e6.
16. Cuzner-Dochan W, Ream E, Norton C. Review article: description and management of fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;37(5):505–16.
17. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: A practical guide for clinicians and researchers. *J Psychosom Res*. 2004;56(2):157–70.
18. Arnett SV, Clark I. Inflammatory fatigue and sickness behaviour—lessons for the diagnosis and management of chronic fatigue syndrome. *J Affect Disord*. 2012;141(2):30–42.
19. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol*. 1998;25 Suppl 3:43–6.
20. Cohen BL, Zolga H, Shah SA, Lelke N, Lidofsky S, Bright R, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther*. 2014;39(8):811–22.
21. Ophelm R, Fagermoen MS, Berniklev T, Jelsness-Jørgensen L-P, Møum B. Fatigue interference with daily living among patients with inflammatory bowel disease. *Qual Life Res*. 2014;23(2):707–17.
22. Norton C, Cuzner-Dochan W, Bassett P, Berliner S, Bredin F, Darvell M, et al. Assessing fatigue in inflammatory bowel disease: comparison of three fatigue scales. *Aliment Pharmacol Ther*. 2015;42(2):203–11.
23. Willert N, Sarter H, Gower-Rousseau C, Adrianjafy C, Olympe A, Buissou A, et al. Patient reported outcomes in a French nationwide survey of inflammatory bowel disease patients. *J Crohns Colitis*. 2017;11(2):165–74.
24. Beck A, Bager P, Jensen PE, Dahlerup JF. How fatigue is experienced and handled by female outpatients with inflammatory bowel disease. *Gastroenterol Res Pract*. 2013;2013:153818.
25. Krijne JE, Lie MRKL, Vogelaa L, van der Woude CJ. Practical guideline for fatigue management in inflammatory bowel disease. *J Crohns Colitis*. 2016;10(1):105–11.
26. Van Langenberg D, Gibson P. Systematic review: fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2010;32(2):131–43.
27. Cuzner-Dochan W, Dibley LB, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: an exploratory study. *J Adv Nurs*. 2013;69(9):1987–99.
28. Cuzner-Dochan W, Norton C, Bredin F, Darvell M, Nathan I, Terry H. Healthcare professionals' perceptions of fatigue experienced by people with IBD. *J Crohns Colitis*. 2014;8(8):835–44.
29. Graff LA, Clara I, Walker JR, Lix L, Carr R, Miller N, et al. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clin Gastroenterol Hepatol*. 2013;11(9):1140–6.
30. Vogelaa L, van't Spijker A, van Tilburg AJ, Kuipers EJ, Timman R, van der Woude CJ. Determinants of fatigue in Crohn's disease patients. *Eur J Gastroenterol Hepatol*. 2013;25(2):246–51.
31. van Langenberg DR, Gibson PR. Factors associated with physical and cognitive fatigue in patients with Crohn's disease: a cross-sectional and longitudinal study. *Inflamm Bowel Dis*. 2014;20(1):115–25.
32. Jelsness-Jørgensen LP, Berniklev T, Henriksen M, Torp R, Møum BA. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis*. 2011;17(7):1564–72.
33. Bager P, Befrits R, Wikman O, Lindgren S, Møum B, Hjortswang H, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther*. 2012;35(1):133–41.
34. Yoo S, Jung YS, Park JH, Kim HJ, Cho YK, Sohn CJ, et al. Fatigue severity and factors associated with high fatigue levels in Korean patients with inflammatory bowel disease. *Gut Liver*. 2014;8(2):148.
35. Grimstad T, Norheim KB, Isaksen K, Leita K, Hetta AK, Carlsen A, et al. Fatigue in newly diagnosed inflammatory bowel disease. *J Crohns Colitis*. 2015;9(9):725–30.
36. Kalaitzakis E, Carlsson E, Josefsson A, Bosaeus I. Quality of life in short-bowel syndrome: impact of fatigue and gastrointestinal symptoms. *Scand J Gastroenterol*. 2008;43(9):1057–65.
37. Banovic I, Gilbert D, Jebrane A, Cosnes J. Diagnostic profiles determined by the CART procedure: IBD patients and fatigue. *J Health Psychol*. 2012;17(4):500–8.
38. Banovic I, Gilbert D, Jebrane A, Cosnes J. Personality and fatigue perception in a sample of IBD outpatients in remission: A preliminary study. *J Crohns Colitis*. 2012;6(5):571–7.
39. Artom M, Cuzner-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. *J Crohns Colitis*. 2016;10(7):860–9.
40. Simén S, Svedlund J, Possner U, Björnsson E, Abrahamsson H. Predictors of subjective fatigue in chronic gastrointestinal disease. *Aliment Pharmacol Ther*. 2008;28(5):638–47.
41. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manag*. 2009;37(1):107–28.
42. Vogelaa L, van't Spijker A, Vogelaa T, van Buschbach JJ, Visser MS, Kuipers EJ, et al. Solution focused therapy: A promising new tool in the management of fatigue in Crohn's disease patients: Psychological interventions for the management of fatigue in Crohn's disease. *J Crohns Colitis*. 2011;5(6):585–91.
43. Costantini A, Pala M. Thiamine and fatigue in inflammatory bowel diseases: an open-label pilot study. *J Altern Complement Med*. 2013;19(8):704–8.
44. Vogelaa L, van't Spijker A, Timman R, van Tilburg AJ, Bac D, Vogelaa T, et al. Fatigue management in patients with IBD: a randomised controlled trial. *Gut*. 2014;63(6):911–8.
45. McNelly A, Nathan I, Monte M, Grimb G, Norton C, Bredin F, et al. PTU-064 Inflammatory bowel disease and fatigue: the effect of physical activity and/or omega 3 supplementation. *Trials*. 2015;16 Suppl 1:A88–A.
46. Lichtenstein GR, Bala M, Han C, DeWoody K, Schaible T. Infliximab improves quality of life in patients with Crohn's disease. *Inflamm Bowel Dis*. 2002;8(4):237–43.
47. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? *World J Gastroenterol*. 2007;13(14):2089–93.
48. Loftus EV, Feagan BG, Colomb J-F, Rubin DT, Wu EQ, Andrew PY, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol*. 2008;103(12):3132–41.
49. Hetzel D, Ford D, Dahl N, Strauss W. P437 Intravenous (IV) ferumoxytol (FER) for the treatment of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD): Efficacy, safety and health-related quality of life (HRQOL). *J Crohns Colitis*. 2014;8(Supplement 1):S248–9.
50. Grimstad T, Norheim KB, Kvaloy JT, Isaksen K, Leita K, Carlsen A, et al. Conventional treatment regimens for ulcerative colitis alleviate fatigue – an observational cohort study. *Scand J Gastroenterol*. 2016;51(10):1213–9.
51. Vogelaa L, Van den Berg-Elmors R, Bussmann H, Rozenberg R, Timman R, Van der Woude CJ. Physical fitness and physical activity in fatigued and non-fatigued inflammatory bowel disease patients. *Scand J Gastroenterol*. 2015;50(11):1357–67.
52. Garcia-Vega E, Fernandez-Rodriguez C. A stress management programme for Crohn's disease. *Behav Res Ther*. 2004;42(4):367–83.
53. Boye B, Lundin KE, Jantschek G, Leganger S, Møkleby K, Tangen T, et al. INSPIRE study: Does stress management improve the course of inflammatory bowel disease and disease-specific quality of life in distressed patients with ulcerative colitis or Crohn's disease? A randomized controlled trial. *Inflamm Bowel Dis*. 2011;17(9):1863–73.
54. Van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *J Psychosom Res*. 2006;61(5):583–5.
55. Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. *Clin Psychol Rev*. 2007;21(7):781–97.

56. Hewlett S, Chalder T, Choy E, Cramp F, Davis B, Dures E, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology*. 2011; 50(6):1004–6.
57. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosom Med*. 2008;70(2):205–13.
58. Hewlett S, Ambler N, Almeida C, Cliss A, Hammond A, Kitchen K, et al. Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. *Ann Rheum Dis*. 2011;70(6):1060–7.
59. Montgomery GH, David D, Kangas M, Green S, Sucala M, Bovbjerg DH, et al. Randomized controlled trial of a cognitive-behavioral therapy plus hypnosis intervention to control fatigue in patients undergoing radiotherapy for breast cancer. *J Clin Oncol*. 2014;32(6):557–63.
60. Hofmann SG, Asnaani A, Vonk WJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. *Cogn Ther Res*. 2012;36(5):427–40.
61. Giessens MF, Verhagen S, Wiltjes F, Blijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *J Clin Oncol*. 2006;24(30):4882–7.
62. Thomas PW, Thomas S, Kersten P, Jones R, Nock A, Slingsby V, et al. Multi-centre parallel arm randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based cognitive behavioural approach to managing fatigue in people with multiple sclerosis. *BMC Neurol*. 2010;10(1):1.
63. Thomas S, Thomas PW, Kersten P, Jones R, Green C, Nock A, et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1092–9.
64. Thomas PW, Thomas S, Kersten P, Jones R, Slingsby V, Nock A, et al. One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *BMC Neurol*. 2014;14(1):1.
65. Wahed M, Corser M, Goodhand JR, Rampton DS. Does psychological counseling alter the natural history of inflammatory bowel disease? *Inflamm Bowel Dis*. 2010;16(4):664–9.
66. Keefe L, Doerfler B, Artz C. Optimizing management of Crohn's disease within a project management framework: results of a pilot study. *Inflamm Bowel Dis*. 2012;18(2):254–60.
67. von Wiersheim J, Kessler H. Psychotherapy with chronic inflammatory bowel disease patients: a review. *Inflamm Bowel Dis*. 2006;12(12):1175–84.
68. Goodhand JR, Wahed M, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? *Expert Rev Gastroenterol Hepatol*. 2009;3(6):661–79.
69. Timmer A, Preiss JC, Motschall E, Rücker G, Jantschek G, Moser G. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev*. 2011;2:CD006913.
70. Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. *Inflamm Bowel Dis*. 2013;19(12):2704–15.
71. McCombie AM, Mulder RT, Geary RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohns Colitis*. 2013;7(12):935–49.
72. Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189–99.
73. McCombie A, Geary R, Mulder R. Preferences of inflammatory bowel disease patients for computerised versus face-to-face psychological interventions. *J Crohns Colitis*. 2014;8(6):536–42.
74. McCombie A, Geary R, Andrews J, Mulder R, Mikocka-Walus A. Does computerized cognitive behavioral therapy help people with inflammatory bowel disease? A randomized controlled trial. *Inflamm Bowel Dis*. 2016;22(1):171–81.
75. Farrell D, Savage E, Norton C, Jelsness-Jørgensen LP, Czauber-Dochan W, Artom M. Interventions for fatigue in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2015;12:CD012005.
76. Hackett KL, Lambson RL, Strassheim V, Gotts Z, Deary V, Newton JL. A concept mapping study evaluating the UK's first NHS generic fatigue clinic. *Health Expect*. 2016;19(5):1138–49.
77. Uppke S, Ziegelmann JP. Theory-based health behavior change: Developing, testing, and applying theories for evidence-based interventions. *Appl Psychol*. 2008;57(4):698–716.
78. Jones D, Gray J, Newton J. Perceived fatigue is comparable between different disease groups. *QJM*. 2009;102(9):617–24.
79. Kwakkenbos L, Minton O, Stone PC, Alexander S, Baron M, Hudson M, et al. Can the cancer-related fatigue case-definition criteria be applied to chronic medical illness? A comparison between breast cancer and systemic sclerosis. *J Rheumatol*. 2015;42(7):1156–62.
80. Czauber-Dochan W. Exploring fatigue in inflammatory bowel disease as experienced by individuals – a descriptive phenomenological study. London: King's College London; 2015.
81. Kroencke DC, Lynch SG, Denney DR. Fatigue in multiple sclerosis: relationship to depression, disability, and disease pattern. *Mult Scler*. 2000;6(2):131–6.
82. Pollard L, Choy E, Gonzalez J, Khoshaba B, Scott D. Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology*. 2006;45(7):885–9.
83. Artom M, Czauber-Dochan W, Sturt J, Murrells T, Norton C. The contribution of clinical and psychosocial factors in inflammatory bowel disease-fatigue: a cross-sectional study to fatigue in 182 patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2016;43(3):403–16.
84. Skerrett TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *J Psychosom Res*. 2006;61(5):587–93.
85. Boivin A, Curie K, Fervers B, Gracia J, James M, Marshall C, et al. Patient and public involvement in clinical guidelines: international experiences and future perspectives. *Qual Saf Health Care*. 2010;19(5):1–4.
86. Brett J, Stanisewska S, Mockford C, Hieron-Max S, Hughes J, Tysall C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Health Expect*. 2014;17(5):637–50.
87. Levenhail H, Meyer D, Nerenz D. The common sense representation of illness danger. *Contrib Med Psychol*. 1980;27–30.
88. Knoop H, Van Kessel K, Moss-Morris R. Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychol Med*. 2012;42(01):205–13.
89. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
90. Eldridge S, Bond C, Campbell M, Hopewell S, Thabane L, Lancaster G, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: using consensus methods and validation to develop a conceptual framework. *Trials*. 2015;16(2):1.
91. Thabane L, Ma J, Chu R, Cheng J, Ismail A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*. 2010;10(1):1.
92. Whitehead AL, Sully BG, Campbell MJ. Pilot and feasibility studies: Is there a difference from each other and from a randomised controlled trial? *Contemp Clin Trials*. 2014;38(1):130–3.
93. Lee EC, Whitehead AL, Jacques RM, Julious SA. The statistical interpretation of pilot trials: should significance thresholds be reconsidered? *BMC Med Res Methodol*. 2014;14(1):41.
94. Ioannidis JP, Greenland S, Hlatky MA, Khouri MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet*. 2014;383(9912):166–75.
95. O'Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Hewison J. What can qualitative research do for randomised controlled trials? A systematic mapping review. *BMJ Open*. 2013;3(6):e002889.
96. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ*. 2015;350:h1258.
97. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol*. 2010;10(1):67.
98. Christensen LB, Johnson B, Turner LA. Research methods, design, and analysis. Boston: Allyn & Bacon; 2011.
99. Ammerman A, Smith TW, Calancie L. Practice-based evidence in public health: improving reach, relevance, and results. *Annu Rev Public Health*. 2014;35:47–63.
100. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *BMJ*. 2009;339:b3496.
101. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med*. 2010;8(1):1.
102. O'Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Goode J, Hewison J. Maximising the value of combining qualitative research and

- randomised controlled trials in health research: the QUALitative Research in Trials (QUART) study—a mixed methods study. *Health Technol Assess.* 2014;18(38):1–197.
103. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ.* 2008;337:a2390.
104. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. *Behav Res Ther.* 2012;50(6):415–21.
105. Giacomini MK, Cook DJ, for the Evidence-Based Medicine Working G. Users' guides to the medical literature: Xiii. qualitative research in health care a. are the results of the study valid? *JAMA.* 2000;284(3):357–62.
106. Côté L, Turgeon J. Appraising qualitative research articles in medicine and medical education. *Med Teach.* 2005;27(1):71–5.
107. Midgley N, Ansaldo F, Target M. The meaningful assessment of therapy outcomes: Incorporating a qualitative study into a randomized controlled trial evaluating the treatment of adolescent depression. *Psychotherapy.* 2014;51(1):128.
108. Fereday J, Muir-Cochrane E. Demonstrating rigor using thematic analysis: A hybrid approach of inductive and deductive coding and theme development. *Int J Qual Methods.* 2006;5(1):80–92.
109. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised controlled trials of complex interventions. *BMJ.* 2006;332(7538):413–6.
110. Cauber-Dochan W, Norton C, Bassett P, Berliner S, Bredin F, Danell M, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *J Crohns Colitis.* 2014;8(11):1396–406.
111. W-y C, Garratt AM, Russell IT, Williams JG. The UK IBDQ—a British version of the inflammatory bowel disease questionnaire: development and validation. *J Clin Epidemiol.* 2000;53(3):297–306.
112. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology.* 1989;96(3):804–10.
113. Hoivik ML, Bekkevold T, Moum B. Need for standardization in population-based quality of life studies: A review of the current literature. *Inflamm Bowel Dis.* 2010;16(3):525–36.
114. Harvey R, Bradshaw J. A simple index of Crohn's-disease activity. *Lancet.* 1980;315(8167):514.
115. Wainsley R, Ayres R, Pounder R, Allan R. A simple clinical colitis activity index. *Gut.* 1998;43(1):29–32.
116. Broadbent E, Petrie K, Weinman J. The Brief Illness Perception Questionnaire (BIPQ): validity and reliability. *Int J Behav Med.* 2004;11:278.
117. Moss-Morris R, Weinman J, Petrie K, Horne R, Cameron L, Buick D. The revised illness perception questionnaire (IPQ-R). *Psychol Health.* 2002;17(1):1–16.
118. Knowles S, Wilson J, Connell W, Kamm M. Preliminary examination of the relations between disease activity, illness perceptions, coping strategies, and psychological morbidity in Crohn's disease guided by the common sense model of illness. *Inflamm Bowel Dis.* 2011;17(12):2551–7.
119. de Raaij EJ, Schröder C, Maissan FJ, Pool JJ, Wittink H. Cross-cultural adaptation and measurement properties of the brief illness perception questionnaire-Dutch language version. *Man Ther.* 2012;17(4):330–5.
120. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14(6):540.
121. Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev.* 2006;10(1):63–76.
122. Chervin R. Epworth sleepiness scale? *Sleep Med.* 2003;4(3):175.
123. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092–7.
124. Quick VM, McWilliams R, Byrd-Bredbenner C. Case-control study of disturbed eating behaviors and related psychographic characteristics in young adults with and without diet-related chronic health conditions. *Eat Behav.* 2012;13(3):207–13.
125. Cooper CL, Hind D, Parry GD, Isaac CL, Dimairo M, O'Cathain A, et al. Computerised cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: external pilot trial. *Trials.* 2011;12(1):1–14.
126. Glozier N, Christensen H, Naismith S, Cockayne N, Donkin L, Neal B, et al. Internet-delivered cognitive behavioural therapy for adults with mild to moderate depression and high cardiovascular disease risks: a randomised attention-controlled trial. *PLoS One.* 2013;8(3):e59139.
127. Clark DM. Implementing NICE guidelines for the psychological treatment of depression and anxiety disorders: the IAPT experience. *Int Rev Psychiatry.* 2011;23(4):318–27.
128. Kroenke K, Spitzer R, Williams J. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–13.
129. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. *Med Care.* 2004;42(12):1194–201.
130. Persoons P, Luyckx K, Fischler B. Psychiatric diagnoses in gastroenterology: Validation of a self-report instrument (PRIME-MD Patient Health Questionnaire), epidemiology and recognition. *Gastroenterology.* 2001;120(5):A114.
131. Lee KA, Zaffke ME. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. *J Obstet Gynecol Neonatal Nurs.* 1999;28(2):183–91.
132. Elkjaer M, Shuhaibar M, Burisch J, Bailey Y, Scherfig H, Laugesen B, et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. *Gut.* 2010;59(12):1652–61.

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5.9 Telephone intervention modality

Conventional wisdom supports the idea that psychological therapies should be delivered face-to-face. The central premise to this argument is that the effectiveness of such interventions depends upon on the development of a high quality therapeutic alliance between therapist and client. As the use of the telephone invariably eliminates cues and information transmitted through verbal and non-verbal channels, the telephone could potentially impact on the development of therapeutic alliance (Mohr et al., 2012, Sarkar and Gupta, 2012). However, in a study comparing therapeutic alliance in clients receiving CBT for depression by telephone or fact-to-face (Stiles-Shields et al., 2014), there were no significant differences in client or therapist alliance on the Working Alliance Inventory and Working Alliance Inventory scores predicted depression end of treatment outcomes. Findings on the comparability of therapeutic alliance levels between telephone and face-to-face interventions have also been found for interventions for psychosis (Mulligan et al., 2014). In light of the above data, the decision to use the telephone as the modality of delivery was therefore taken.

The choice of the telephone as the modality of delivery of the intervention was due to its widespread use and its ability to overcome potential geographical barriers. The telephone is the most widely used communication medium in the UK with 94% of adults personally owning/using a mobile phone (OfCom, 2017). Telephone-administered psychotherapy is now increasingly part of the mental health care landscape (Mohr et al., 2008). The telephone offers the opportunity to extend care to populations that are difficult to reach, such as rural populations, patients with chronic illnesses and disabilities, and individuals who otherwise have barriers to treatment (Mohr et al., 2005). Accordingly, the acceptability of delivering care over the telephone is growing. A survey of primary care patients found that nearly 19% of patients who desired behavioural and psychological care wanted telephone treatment and an additional 44% would consider it (Mohr et al., 2010). Furthermore, systematic review of evidence from nine RCTs (1093 participants) of telephone-delivered CBT in patients with long-term conditions reported a mean attrition rate was 9.5% across all the studies (Muller and Yardley, 2011), which is significantly lower than the attrition rate in studies delivering CBT face-to-face (Salmoiraghi and Sambhi, 2010).

5.10 Feasibility outcomes

The MRC guidance (Craig et al., 2008) states that the purpose of the pilot and feasibility phase of the framework is to inform the design of a subsequent large, definitive trial assessing the effectiveness of the intervention. Pilot studies are a smaller version of the main study that test whether the components of the main study can all work together (Thabane et al., 2010). They are a requisite initial step in exploring a novel intervention (Whitehead et al., 2014) and resemble the main study in many respects, including the assessment of the primary outcome. Pilot studies are

done when an outline plan for the main study has been settled, in order to test whether it can be delivered smoothly and efficiently (Lee et al., 2014). Although, staging of studies is not as well defined in non-drug intervention development, when designing a pilot study it is always important to keep the next study in mind. The aims and methods of the pilot should be aligned with the goals of the subsequent study (Moore et al., 2011). Pilot studies can be subdivided into internal and external pilots. External pilots are independent pieces of work, which are designed and conducted separately from the main trial. Conversely, internal pilot studies are studies which are incorporated within the main trial (Charlesworth et al., 2013). The current study was an external pilot study. An external pilot was chosen as opposed to an internal pilot because it allowed for pre-testing of the feasibility of other factors related to the trial that could not have otherwise be determined if the pilot had been part of the main trial (Lancaster et al., 2001). Furthermore, at the time of planning of the pilot study, the full-scale effectiveness RCT was not yet funded.

Van Teijlingen et al. (2001) and Van Teijlingen and Hundley (2001) summarise the reasons for performing pilot studies into four broad classifications: process, resources, management and scientific. Reasons in the *process* category assess the feasibility of the steps that need to take place as part of the large-scale trial. Reasons in the *resources* category assess time and budget problems that can occur during the large-scale trial. Reasons in the *management* category cover personnel and data management issues. Lastly, reasons in the *scientific* category deal with estimation of treatment effect, levels of response and treatment safety (Thabane et al., 2010). The feasibility outcomes of the pilot study were part of the *process* classification and had the purpose of assessing the potential successful implementation of the intervention in a large-scale trial and to reduce threats to the validity of the large-scale trial in the future (Tickle-Degnen, 2013). Collecting information relating to these feasibility outcomes reduces the likelihood of failure of a future large-scale trial due to poor design (Wilson et al., 2015). The feasibility outcomes for this pilot study were selected to be in line with the methodological issues that require piloting in the context of an RCT according to Shanyinde and colleagues (2011). These feasibility outcomes were to:

- Assess the feasibility of recruiting eligible patients and assess the willingness of participants to be randomised;
- Assess the completeness of the outcome data questionnaire booklets;
- Evaluate the compliance rates of patients to the intervention;
- Assess withdrawal rates during the intervention support sessions; assess the completion rates of the outcome measures at follow-up.

Testing the acceptability of randomisation can determine the acceptability of the concept of randomisation to the participant and the best way of explaining the process to the patient before

eliciting informed consent. Likewise it is crucial to determine what the consent rate will be for patients enrolling in the trial as this will impact directly on planning the time needed to recruit enough participants to the trial, with consequent implications for funding. Moreover, failure to recruit the required number of participants reduces the statistical power, with consequent implications for determining effect sizes. Piloting of outcome data questionnaire booklets is especially important when the patient has to self-complete the questionnaires as this will ensure that the questionnaires are comprehensible and appropriate, and that the questions are clearly understood, well defined and presented in a coherent way (Lancaster et al., 2001). Lastly, compliance and withdrawal rates from the intervention need to be assessed as attrition rates have been found to be significantly associated with poor outcomes in low intensity psychological interventions (Delgadillo et al., 2014).

Progress criteria for success were defined for the primary feasibility objectives of the study. These helped to interpret the results of the pilot study and determine whether it is feasible to proceed to a full-scale trial. Following Thabane and colleagues' (2010) recommendations, the outcome of the pilot study was categorised into one of four options: i) Stop (main study not feasible) ii) continue, but modify protocol (feasible with modifications), iii) continue without modifications, but monitor closely (feasible with close monitoring), and iv) continue without modifications (feasible as is). The success of procedures and unanticipated problems were also carefully examined in order to obtain the best possible design for future large-scale trials of IBD-fatigue management (Shanyinde et al., 2011). Nonetheless, due to the small size of pilot studies it is advised never to use pilot study effect sizes alone to determine whether a full trial should be conducted. Other factors such as qualitative impressions from pilot study participants on how well the intervention worked in the field should also be evaluated. Indeed, if the results of the pilot study reflect promise in every aspect but the observed effect size, the progression to a large scale trial should be considered (Westlund and Stuart, 2016). Consequently, where outcomes fell short of a pre-defined progression criterion except there was a sufficient qualitative understanding of why this happened and how to improve it, the possibility of proceeding should be evaluated (O'Cathain et al., 2015).

5.11 Acceptability outcomes

Guided by a person-based approach to intervention testing (Yardley et al., 2015), acceptability outcomes were included to ground the development of the intervention in a thorough understanding of the perspective and psychosocial context of the individuals who will use it. Indeed eliciting and addressing the views and needs of the intended intervention users is a crucial part of effective intervention testing (Baker et al., 2014) to ensure the intervention is engaging and usable. Utilised to complement theory-based approaches, the person-based approach provides

guidance on the most effective ways of applying theory in the specific context of each intervention and the individuals who will use it. It provides insight into the ways in which participants perceive and utilise specific elements of the intervention and why certain elements may be particularly important to them (Yardley et al., 2015). The acceptability outcomes were to:

- Evaluate patients' experience of the intervention
- Evaluate therapists' views on the intervention delivery
- Evaluate HCPs views on the intervention implementation

5.12 Initial estimates of efficacy outcome measures

A detailed description and justification for the use of the majority of the scales used to test initial estimates of efficacy in the pilot study was included in Chapter 4, Section 4.2 Study Questionnaires. For further information on: IBD-Fatigue Scale, United Kingdom Inflammatory Bowel Disease Questionnaire, Brief Illness Perceptions Questionnaire and Epworth Sleepiness Scale, please refer back to *Sections 4.2.1 to 4.2.6*. The study questionnaires were presented to participants grouped in a booklet (Appendix XVII). Instead of using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), a decision was made to utilise two separate questionnaires for the measurement of depression and anxiety. The HADS is the most commonly utilised measure to assess depression and anxiety in IBD (Neuendorf et al., 2016) and has been extensively used in medical patients (Mikocka-Walus et al., 2016). However, it is yet to be validated in IBD and it has recently been shown to differentiate poorly between anxiety and depression (Cosco et al., 2012, Norton et al., 2013). Furthermore, a systematic review and meta-analysis in rheumatoid arthritis (Dickens et al., 2002) showed significantly greater effect sizes for depression in patients using the HADS compared to other depression scales. Indeed, studies using the HADS found patients with rheumatoid arthritis to be more depressed. The HADS contains items such as "I feel slowed down", "I can sit at ease and feel relaxed", and "I still enjoy the things I used to enjoy" which may overlap with symptoms of patients' physical illness, thus inflating their depression scores.

5.12.1 Nine-item Patient Health Questionnaire (PHQ-9)

The PHQ-9 (Kroenke et al., 2001) was firstly designed to be a diagnostic and severity instrument for depressive symptoms in patients in primary care. The questionnaire contains nine items, which are scored from 0 (not at all) to 3 (nearly every day), according to the frequency of their experience over the previous two-week period, with a total score range of 0 to 27. Major depression is diagnosed if five or more of the nine depressive symptom criteria have been present at least "more than half the days" in the past two weeks, and one of the symptoms is depressed mood or anhedonia. The scale correlates with other validated depression measures including: the Beck

Depression Inventory–II (Titov et al., 2011), the HADS (Kendel et al., 2010) and the Center for Epidemiologic Studies Depression Scale (Milette et al., 2010). The PHQ-9 has been widely applied in medical settings (Kroenke et al., 2010) and its different versions have been utilised for the assessment of depressive symptoms in studies with IBD patients (Cohen et al., 2014, Calloway et al., 2017).

The scale has shown good sensitivity to change, with changes in the PHQ-9 score corresponding to changes in depression diagnostic status over time (Löwe et al., 2004a). Likewise, the PHQ-9 has shown to be a reliable instrument to measure response to depression treatment (Löwe et al., 2004b). It has therefore been deemed as a useful brief tool to be used in longitudinal studies and clinical trials. The PHQ-9 was chosen for the present intervention study as it consists of the actual 9 criteria upon which the diagnosis of Diagnostic and Statistical Manual of Mental Disorders IV depressive disorders is based. Its exclusive focus on depressive disorders ensures accurate discrimination of depression from anxiety and general psychological distress. Furthermore, although it has comparable sensitivity and specificity (Ammann et al., 2014), it is easy to use and half the length of other depression measures (Bombardier et al., 2004). Indeed, brief measures imply less patient burden and are more likely to ultimately be utilised in the busy setting of clinical practice (Kroenke et al., 2001).

5.12.2 Seven-item Generalised Anxiety Disorder Scale (GAD-7)

The GAD-7 (Spitzer et al., 2006) was developed with a primary care population to identify generalised anxiety disorder. It asks participants how often during the last two weeks they have been bothered by each of the seven core symptoms of anxiety. Response options are ‘not at all’, ‘several days’, ‘more than half the days’ and ‘nearly every day’, scored as 0, 1, 2 and 3, respectively. It has a minimum possible score of zero and a maximum possible score of 21. Systematic review evidence (Plummer et al., 2016) suggests a cut-off of eight or nine to optimise sensitivity. The GAD-7 has shown to have high levels of internal consistency and test-retest reliability (Löwe et al., 2008). It has been used in large-scale treatment studies (Clark et al., 2009) and has been shown to be more responsive to change following treatment compared to other scales (Dear et al., 2011). The GAD-7 is thus suitable to be used in brief clinical interventions.

The GAD-7 was chosen for the present intervention study as it is based on Diagnostic and Statistical Manual of Mental Disorders IV criteria and it is easy to administer without undue burden on patients (Ruiz et al., 2011). The scale has previously been used to assess anxiety symptoms in patients with IBD (Byrne et al., 2017). Furthermore, both the PHQ-9 and the GAD-7 form part of the core Improving Access to Psychological Therapy outcome dataset and thus would enable comparison with national data in the future.

5.13 Study follow-up assessment times

Psychosocial intervention studies targeting IBD-fatigue as a primary or secondary outcome have varied in their follow-up assessment times. Garcia-Vega and colleagues (2004) assessed the effects of stress-management post-treatment, at 6 and 12 months post-treatment. Vogelaar and colleagues (2011) assessed the effects of solution-focused therapy and problem solving therapy at 3 months post-treatment. Lastly, Vogelaar and colleagues (2014) assessed the effects of solution-focused therapy at 3, 6 and 9 months post-treatment. More broadly of the 21 studies included in a systematic review of psychological interventions (Timmer et al., 2011), 11 studies had a follow-up period of 12 months or longer, in four studies the last assessment was scheduled at 3 months and in the remaining studies data were reported for time intervals of 4 to 10 months or the exact time point was not specified. No study provided a justification for the choice of follow-up assessment times. It was thus difficult to determine the appropriate study follow-up assessment times based on evidence from similar trials.

The success of RCTs is contingent upon adequate retention of research participants (Friedman et al., 1998) and it is increasingly recognised that performing long-term follow-up RCTs is challenging due to attrition. The likelihood of loss to follow-up increases with the duration of follow-up (Fewtrell et al., 2016). Attrition can be problematic in intervention studies as it can threaten the reliability and validity of the findings by: limiting analyses to a smaller and less representative sample and altering the composition of the intervention groups (Ahern and Le Brocq, 2005). Nonetheless, the 12 months post-randomisation follow-up assessment time was chosen to assess the long-term durability of psychological treatment on IBD-fatigue. No intervention study has previously assessed the effects of psychological treatment on fatigue and QoL at one-year post-randomisation. It was therefore important to determine whether any effects of CBT were maintained over time. The longest follow-up time utilised by a study targeting fatigue as a primary outcome to date was 9 months. In the RCT assessing the efficacy of a 7-session course of solution-focused therapy (Vogelaar et al., 2014), participants showed a greater reduction in fatigue and QoL compared to the care as usual group at 3-months. However at 9 months, the effects were no longer significant ($p=0.66$).

Chapter 6

6 Paper 4 - Cognitive Behavioural Therapy for the Management of Inflammatory Bowel Disease-Fatigue: A Pilot Randomised Controlled Trial

This chapter includes the findings from the pilot RCT, submitted as Paper 4 of this PhD thesis (Artom et al., 2018, submitted). Paper 4 has been submitted for publication in *Trials and Feasibility* journal and is currently under review. A statement of the contribution of the PhD student to this paper appears at the end of the paper on page 162. Amendments to the published paper suggested by the PhD examiners following the oral examination are presented in Appendix XIX.

Pilot and Feasibility Studies
**Cognitive Behavioural Therapy for the Management of Inflammatory Bowel Disease-
Fatigue: A Pilot Randomised Controlled Trial**
--Manuscript Draft--

Manuscript Number:	
Full Title:	Cognitive Behavioural Therapy for the Management of Inflammatory Bowel Disease-Fatigue: A Pilot Randomised Controlled Trial
Article Type:	Research
Funding Information:	
Abstract:	<p>Background Fatigue is the third most prevalent symptom for patients with inflammatory bowel disease (IBD), yet optimal strategies for its management are unclear. Treatment protocols for fatigue in other conditions have been based on cognitive-behavioural models. Targeting cognitions, emotions and behaviour related to fatigue through cognitive-behavioural therapy (CBT) may be a viable option to improve fatigue and quality of life (QoL) in IBD.</p> <p>Methods This single centre, two-arm, pilot randomised controlled trial (RCT) aimed to assess the feasibility and initial estimates of efficacy of a CBT intervention for the management of IBD-fatigue. Feasibility, acceptability and initial estimates of efficacy outcomes were collected through self-report measures and qualitative semi-structured interviews. Participants were recruited from one tertiary referral centre. Intervention Group 1 received a CBT manual for the management of fatigue, one 60-min session and seven 30-min telephone sessions with a therapist over 8 weeks. Control Group 2 received a fatigue information sheet without therapist help. Participants were included if they were not experiencing bowel symptoms associated with a relapse of IBD. A nested qualitative study evaluated patients' and therapists' experiences, and IBD-healthcare professionals' (HCPs) perceptions of the intervention.</p> <p>Results Eighty-nine participants were assessed for eligibility. Of these, 31 of the 70 eligible participants consented to participate (recruitment rate of 44%). Of the 15 participants randomised to the intervention group, 13 (87%) started it and 10 (77% of those who started) completed all 8 sessions. Twenty-two (71%) participants completed baseline and 3-months' follow-up questionnaires. Initial estimates of efficacy with per protocol analysis showed a reduction in fatigue scores and an improvement in QoL scores at 3-months post-randomisation. The difference in change in scores between Group 1 and Group 2 was significant for impact of fatigue (mean difference= -26.89, confidence intervals = -51.39, -2.39, p = .034). The intervention was acceptable to participants and feasible for therapists to deliver. HCPs reported that the intervention would be broadly applicable but time, finance and training constraints may limit its implementation.</p> <p>Conclusions A full-scale effectiveness RCT testing CBT for IBD-fatigue is feasible and has a potential for improvement of fatigue with some changes to the protocol.</p>
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Cognitive Behavioural Therapy for the Management of Inflammatory Bowel Disease-Fatigue: A Pilot Randomised Controlled Trial

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Abstract

Background

Fatigue is the third most prevalent symptom for patients with inflammatory bowel disease (IBD), yet optimal strategies for its management are unclear. Treatment protocols for fatigue in other conditions have been based on cognitive-behavioural models. Targeting cognitions, emotions and behaviour related to fatigue through cognitive-behavioural therapy (CBT) may be a viable option to improve fatigue and quality of life (QoL) in IBD.

Methods

This single centre, two-arm, pilot randomised controlled trial (RCT) aimed to assess the feasibility and initial estimates of efficacy of a CBT intervention for the management of IBD-fatigue. Feasibility, acceptability and initial estimates of efficacy outcomes were collected through self-report measures and qualitative semi-structured interviews. Participants were recruited from one tertiary referral centre. Intervention Group 1 received a CBT manual for the management of fatigue, one 60-min session and seven 30-min telephone sessions with a therapist over 8 weeks. Control Group 2 received a fatigue information sheet without therapist help. Participants were included if they were not experiencing bowel symptoms associated with a relapse of IBD. A nested qualitative study evaluated patients' and therapists' experiences, and IBD-healthcare professionals' (HCPs) perceptions of the intervention.

Results

Eighty-nine participants were assessed for eligibility. Of these, 31 of the 70 eligible participants consented to participate (recruitment rate of 44%). Of the 15 participants randomised to the intervention group, 13 (87%) started it and 10 (77% of those who started) completed all 8 sessions. Twenty-two (71%) participants completed baseline and 3-months' follow-up questionnaires. Initial estimates of efficacy with per protocol analysis showed a reduction in fatigue scores and an improvement in QoL scores at 3-months post-randomisation. The difference in change in scores between Group 1 and Group 2 was significant for impact of fatigue (mean difference = -26.89, confidence intervals = -51.39, -2.39, $p = .034$). The intervention was acceptable to participants and feasible for therapists to deliver. HCPs reported that the intervention would be broadly applicable but time, finance and training constraints may limit its implementation.

Conclusions

A full-scale effectiveness RCT testing CBT for IBD-fatigue is feasible and has a potential for improvement of fatigue with some changes to the protocol.

Trial registration

Registration Trial ISRCTN 17917944, Registered 2 September 2016

Background

Inflammatory bowel disease (IBD) is a group of chronic, inflammatory conditions of the gastrointestinal tract. The two main types are Crohn's disease (CD) and ulcerative colitis (UC) ¹. The clinical course of IBD is marked by exacerbation and remission ^{2,3}. Its cardinal symptoms include diarrhoea, abdominal pain, urgency, tenesmus, weight loss and fatigue. CD may also lead to intestinal obstruction due to fistulae, strictures or abscesses ^{4,5}. IBD affects about 300,000 people in the United Kingdom (UK) ⁶ and 2.2 million people in Europe ⁷. IBD can have a negative impact on quality of life (QoL), with adverse effects on work, relationships and education ⁸. In line with the international expert consensus of the Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative ⁹ on treatment targets for IBD, having a more holistic approach to its management which addresses patient reported outcomes¹⁰ and recognises its psychological burden is thus an important aspect of care ¹¹.

Fatigue is the third most predominant concern for patients with IBD ¹², experienced by 44- 86% of patients with active disease and 22-41% of patients in remission ¹³. As patients struggle with fatigue in-between flare-ups ¹⁴, patients in remission should not be overlooked ¹⁵. Fatigue has been defined as a "persistent overwhelming sense of tiredness, weakness or exhaustion" ¹⁶ that can be mental, physical or both ¹⁷. It can have a negative impact on personal and social life, on work and employment and the ability to think clearly ^{18 19 20}. Fatigue and the development of fatigue-management interventions are currently top IBD-research priorities in the UK ²¹ and in Europe ²². However, fatigue is only identified and managed in a small proportion of those affected ²³. The aetiology of fatigue is not well understood ^{13, 24}. Inflammation ²⁵, disease activity ^{26 27 17} and anaemia ^{28 29 25} can be predictive of fatigue. IBD-fatigue has also been linked to psychosocial factors including: depression and anxiety ^{17 30 31}, negative perceptions, cognitions and behaviours ³², and sleep problems ^{33, 34 30 35}. Yet in a significant proportion of people there is no physiological explanation for their fatigue ³⁶ and the ways in which clinical and psychosocial factors interact with each other to cause fatigue have rarely been explored ³².

Optimal strategies for the management of IBD-fatigue are unknown and fatigue has seldom been the primary outcome of trials ^{37, 38 39 40 41}. Some benefits have been shown by pharmacological interventions utilising biologics ^{42 43 44}, thiamine ⁴⁰ and ferumoxytol ⁴⁵. However, it is unclear whether these results were due to a direct effect on fatigue or a reduction in inflammation in patients with active disease ⁴⁶. The only trial ³⁹ examining the effect of physical activity, provided inconclusive results. Psychosocial interventions, including stress-management ⁴⁷, solution focused therapy ^{37, 38} and brief behavioural therapy for sleep ⁴⁸ have shown promising effects but which have declined over time. As there are similarities between the perceived experiences of fatigue in different long-term conditions ^{13, 49, 50}, integrating current best evidence across conditions can help to identify effective interventions for IBD-fatigue and their underlying mechanisms ⁵¹ without "reinventing the wheel" ⁵². The majority of psychological treatment protocols in other conditions have been based on cognitive-behavioural models ⁵³⁻⁵⁵, according to which symptoms are maintained by maladaptive cognitive and behavioural factors ⁵⁶.

Disease-related or clinical factors trigger fatigue; the ways in which people respond cognitively, emotionally and behaviourally to their fatigue may then contribute to the perpetuation or worsening of symptoms⁵³. The targeting of cognitions, emotions and behaviour related to fatigue through cognitive-behavioural therapy (CBT) may therefore be a viable option to improve clinical and psychosocial outcomes⁵⁷.

Systematic reviews have appraised psychological interventions for people with IBD^{58 59 60 61 62 63} with encouraging results for CBT on outcomes including relapse reduction⁶⁴, disease course alteration^{65 66}, stress management⁶⁷ and QoL improvement⁶⁸. Although CBT has not been used for fatigue, results from our recent study³² show that the ways patients perceive, interpret and react to fatigue symptoms in IBD are largely comparable to patients with other conditions such as multiple sclerosis (MS)⁶⁹. IBD-patients who have more negative perceptions of fatigue and higher levels of maladaptive behaviours have significantly greater fatigue levels³². Furthermore in a recent qualitative study, people with IBD described an all or nothing behavioural response, where they felt fatigued because they took on more whilst feeling well to compensate in advance for future periods of reduced functioning⁷⁰. A CBT manual developed by Van Kessel et al.⁷¹ for MS was therefore used as the foundation of the intervention for the current study. It was chosen for its promising results in reducing fatigue with MS patients^{71 72}, its strong theoretical grounding in a CBT model⁷³ and its valuable in-depth mediation analysis of processes of change⁷⁴. In the original study, 72 patients with MS-fatigue were randomised to 8 weekly, 50-minutes face-to-face sessions of CBT or relaxation training (RT). The CBT group reported significantly greater reductions in fatigue 9 months post-intervention compared to the RT group, with calculated effect sizes from baseline to the end of treatment of 3.03 for the CBT group and 1.83 for the RT group.

In the current study the UK Medical Research Council (MRC) framework for the development of complex interventions⁷⁵ was utilised to guide the development of the intervention. Its content was based on cognitive-behavioural theory and was grounded in empirical evidence from our previous systematic reviews^{50, 76}, qualitative^{13, 24, 49} and quantitative studies in IBD-fatigue³²; and studies on MS-fatigue^{71, 72}. Iterative work with patients and healthcare professionals (HCPs) took place to tailor the intervention to IBD patients' needs. A telephone intervention was chosen to avoid time and travel burden for patients attending face-to-face sessions and high attrition rates and low compliance to online interventions^{66, 77}. Telephone-delivered CBT has been shown to be effective in patients with long-term conditions, attrition rates are also significantly lower compared to face-to-face interventions⁷⁸. Following the MRC guidelines, the current pilot study was conducted to inform the development of a definitive full-scale effectiveness RCT. A nested qualitative component was included in the study to give contextual data and an explanation of the findings by evaluating patients', therapists' and HCPs' perceptions of the intervention and make alterations to the CBT protocol if required to enhance its acceptability in a full-scale effectiveness trial.

The pilot study aimed to assess the feasibility and initial estimates of efficacy of a CBT intervention for the management of fatigue in patients with IBD. The specific research questions for the study were: 1) What is the feasibility and acceptability of a CBT intervention for the management of fatigue in patients with IBD? 2) What is the feasibility of the trial protocol for delivering a full-scale pragmatic RCT? 3) What are the initial estimates of efficacy of an intervention for the management of fatigue in patients with IBD?

Methods

Design

The study was a single centre, two-arm, pilot RCT. Participants were randomised to either: intervention Group 1 (CBT manual for the management of fatigue, one 60-min session and seven 30-min telephone/Skype sessions with a therapist over an eight-week period); or control Group 2 (a short fatigue information sheet to use without therapist help). A nested qualitative study evaluated patient and therapist experiences, and HCPs perceptions of the intervention. The full protocol of the study reported in this paper is published elsewhere ⁷⁹.

Ethical approval

The study was granted ethical approval by the United Kingdom National Research Ethics Service - North West - Liverpool Central Committee (16/NW/0791). The trial was registered on the ISRCTN registry (17917944) on 02 September 2016.

Patient and Public Involvement (PPI)

All study information, including Patient Information Sheets, Patient Consent Forms and questionnaire booklets, was developed with PPI to ensure acceptability and ease of understanding of what was asked of the participants. The study was approved by the hospital's Gastroenterology Project Board Steering Committee where patients with IBD, HCPs and researchers working in IBD assessed the acceptability and feasibility of the trial protocol. A group of Patient and Public Involvement participants were mailed a draft of the intervention manual together with a Feedback Form in which they were asked to provide feedback on specific questions regarding the language and comprehension, format and organisation, usefulness of the manual and feasibility of the intervention. All suggested changes that made the study more acceptable to patients without compromising its robustness or validity were incorporated in the manual. The Crohn's and Colitis United Kingdom (CCUK) fatigue information sheet was developed by members of UK's leading charity for patients with CD and UC together with members of our research team (CN, WCD).

Setting and participants

Patients were recruited from IBD outpatient clinics at a single, tertiary referral, specialist hospital site between April and August 2017. Patients were included if they had a diagnosis of IBD, self-reported

1 experiencing fatigue and were aged 18 or over. Patients were excluded if they were currently
2 experiencing bowel symptoms they would associate with a relapse of their disease, had CBT for fatigue
3 in the last year, were enrolled in a trial involving a non-licensed pharmacological intervention, pregnant
4 or planning a pregnancy or were unable to give informed consent. A full list of inclusion and exclusion
5 criteria is included in the protocol ⁷⁹.

6 7 8 *Recruitment*

10 Patients were referred by their HCPs and were then provided with the study information by the study
11 researcher. Those interested in the RCT were screened for full eligibility. If ineligible, reasons for
12 ineligibility were recorded. Eligible patients were given at least 48 hours to consider their participation
13 in the study. A mutually convenient time was arranged for a study researcher to answer any additional
14 questions, verify their understanding of what the study involved and confirm their interest in study
15 participation. Reasons for refusal to participate were recorded. Participants who agreed to take part in
16 the study were asked to return signed consent forms and baseline questionnaires in the pre-paid stamped
17 addressed reply envelope provided within 7 days of receipt. Screening and recruitment continued until
18 the target sample size of 30 was reached.

20 21 22 *Randomisation*

23 Randomisation was performed after participants had given informed consent and had completed and
24 returned the baseline questionnaires. Participants were randomly allocated to one of two research arms:
25 CBT manual plus therapist support or fatigue information sheet only. Participants were randomised at
26 the individual level using a random number generator with a 1:1 ratio in the Statistical Package for the
27 Social Sciences (SPSS) Version 22. The randomisation sequence was generated electronically by an
28 independent statistician who had no patient contact prior to the commencement of the study. The trial
29 coordinator (blinded until this point) subsequently accessed the randomisation database to assign
30 participants to the two groups. The participants, the researchers and the therapists were not blinded to
31 treatment allocation after randomisation. Access to usual care, including a hospital-based nurse-led
32 helpline was retained throughout the trial.

33 34 35 *MODIFY Fatigue Intervention*

36 37 38 **CBT manual for IBD-fatigue**

39 The CBT manual used in this trial was adapted from the CBT manual for MS-fatigue management
40 developed by Van Kessel et al. ⁷¹. Participants received a printed copy of the manual in post. The
41 intervention manual included a contents page, an introduction section with instructions for participants,
42 8 topic specific sessions and homework tasks sheets. The manual (94 pages) was presented in a
43 transparent ring binder and each session was colour-coded to facilitate ease of use. The sessions
44 included: IBD fatigue explained; CBT for IBD fatigue; activity scheduling; improving your sleep;

1 understanding IBD symptoms; changing your thinking; managing stress, determining a sense of control
2 and coping with emotions; social support and preparing for the future. The content of the manual was
3 adapted with the help of one of the investigators of the original MS trials^{71, 72}, people with IBD-fatigue,
4 consultant gastroenterologists and IBD-nurse specialists working with people with IBD. A medical
5 writer and a graphic designer aided in making the language and the manual design as user-friendly as
6 possible. Full-details of the manual development and refinement are presented in the intervention
7 protocol⁷⁹.

11 **Intervention Group 1 (CBT manual + therapist)**

12 Participants in intervention Group 1 received the CBT manual for the management of fatigue, this
13 included one 60-minute and seven 30-minute individual telephone sessions with a therapist over an 8-
14 week period. The intervention support sessions were delivered by one of two qualified CBT therapists
15 who had experience of delivering interventions to patients with long-term conditions. Therapists were
16 external, non-NHS, privately contracted and paid at the standard CBT hourly rate. Telephone sessions
17 had the purpose to support the participant in collaboratively develop goals for each session using the
18 information and resources included in the CBT manual.

26 **Control Group 2 (CCUK fatigue information sheet only)**

27 Participants in Group 2 received the CCUK "Fatigue in IBD" Information Sheet (4 pages) to use without
28 therapist help. Participants received the Information Sheet after randomisation at the same time as
29 intervention Group 1 received the CBT manual. The Information Sheet provides a definition of fatigue,
30 an explanation of what may cause it and ways to potentially reduce it <http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/fatigue-and-IBD.pdf>

37 *Minimising bias*

38 A series of steps were taken to minimise bias or systematic errors and to improve trial rigour: the
39 randomisation sequence was generated by an independent statistician who was not involved in the
40 operating of the trial to avoid contamination; the support sessions were delivered by two independent
41 therapists to minimise allegiance bias where results are contaminated by the therapists' experience⁸⁰;
42 qualitative interviews were conducted after the quantitative data collection to avoid potentially
43 influencing participants' experience of the treatment⁸¹; qualitative interviews were analysed by four
44 independent researchers to avoid researchers' biases and enhance confidence in the findings^{82, 83}.

52 *Feasibility and acceptability outcomes*

53 Feasibility and acceptability outcomes, their methods of assessment and progression criteria are
54 summarised in Table 1.

Table 1: Feasibility and acceptability outcomes.

Outcome	Objectives	Methods	Progression criteria
Recruitment	Assess the feasibility of recruiting eligible patients; assess the willingness of participants to be randomised	Recruitment log; screening log; record of reasons for participation refusal	≥50% of eligible participants consented for participation in the study
Completeness of outcome data measures	Assess the completeness of the outcome data questionnaire booklets	Outcome data questionnaire booklets	≤10% missing data in each completed questionnaire booklet
Compliance	Evaluate the compliance rates of patients to the intervention	Post-intervention follow-up questionnaire with patients; semi-structured interviews with therapists	90% of participants read all the sessions of the manual; ≥15 minutes per week spent completing tasks in relation to the intervention
Retention	Assess withdrawal rates during the intervention support sessions; assess the completion rates of the outcome measures at follow-up	Recruitment log therapist session log of patients' compliance; semi-structured interviews with patients	≥80% of those consented will start the intervention; ≥70% of participants who started completed all 8 therapist support sessions; ≤20% of participants withdrew from the intervention support sessions; ≥70% of participants completed baseline and 3-months follow-ups
Delivery	Evaluate therapists' views on the intervention delivery	Semi-structured interviews with therapists	Positive opinions from the therapists regarding the feasibility of delivering the intervention
Implementation	Evaluate HCPs views on the intervention implementation	Semi-structured interviews with HCPs working with people with IBD	Support from HCPs regarding the feasibility of implementation of the intervention
Acceptability of the intervention	Evaluate patients' experience of the intervention	Semi-structured interviews with a sub-set participants in Group 1; post-intervention follow-up questionnaire	Positive opinions from patients regarding an acceptably positive experience of taking part in the intervention

Key: IBD- inflammatory bowel disease; HCPs- healthcare professionals

The feasibility of recruiting participants and willingness to be randomised was evaluated by calculating the proportions of those invited for participation in the study who were eligible and who decided to take part in the trial, together with reasons for ineligibility and participation refusal. The completeness of data collected was assessed by reviewing the proportion of pages and proportion of items of the outcome measure booklets that were completed by the participants. Concordance rates were assessed through a post-intervention follow-up participant questionnaire asking participants about the number of sessions

of the manual they read, the number of telephone therapist support sessions they completed and the time per week they spent completing tasks in relation to the intervention. Therapists were instructed to keep a log recording how many sessions were completed by each participant, the frequency of the sessions and participant-interruptions or withdrawals from the interventions. Completion rates of baseline and outcome measures at 3-months post-randomisation were recorded.

Initial estimates of efficacy outcomes

Participants completed self-report questionnaires at baseline and 3-months post-randomisation. Baseline measures were completed by eligible participants prior to randomisation. All questionnaire booklets were sent by post with pre-paid stamped addressed reply envelopes. At 3-months post-randomisation, participants were posted the full set of outcome measures completed at baseline, together with a post-intervention questionnaire on their experience of the intervention.

Baseline data

At baseline, socio-demographic and clinical data about participations were collected. Gender, age, education status, marital status, employment status and living arrangements were self-reported by participants. IBD diagnosis, latest measurement of faecal calprotectin concentration, IBD-related medications, length of time since diagnosis (months), IBD-related surgeries, smoking status (current smoker, ex-smoker, never smoked), exercise status (< or > 30 minutes of aerobic exercise per week), haemoglobin, ferritin, serum albumin, C-reactive protein (CRP), platelets count, Vitamin B12 and folate were retrieved from patients' hospital records. Clinical data are routinely collected as part of standard care. When data within 3 months before or after baseline questionnaire completion were not present, no additional blood tests were conducted and data were marked as missing.

Outcome measures

Outcome measures were utilised to assess initial estimates of efficacy of Group 1 (CBT manual + therapist support) compared to Group 2 (fatigue information sheet Only). All outcome measures were validated for self-completion. A detailed description and justification for the chosen measures is provided in the protocol of the intervention ⁷⁹. Fatigue and QoL were the primary and secondary outcome measures for the intervention. The IBD-Fatigue (IBD-F) scale ⁸⁴ was utilised to assess frequency, severity, experience and impact of fatigue. The IBD-F is an IBD-specific fatigue scale designed to identify issues of specific importance to people with IBD-fatigue. The United Kingdom Inflammatory Bowel Disease Questionnaire (UK IBDQ) ⁸⁵ was utilised to assess IBD-specific QoL.

Disease activity, perceptions of fatigue (Brief Illness Perceptions Questionnaire [BIPQ]) ⁸⁶, levels of daytime sleepiness (Epworth Sleepiness Scales [ESS]) ⁸⁷, anxiety (7-item Generalised Anxiety Disorder [GAD7] scale) ⁸⁸ and depression (9-item Patient Health Questionnaire [PHQ9]) ⁸⁹ were assessed as explanatory variables for the intervention. The Harvey Bradshaw Index (HBI) ⁹⁰ and the Simple Clinical

Colitis Activity Index (SCCAI)⁹¹ were utilised to measure disease activity for CD and UC participants respectively.

Sample size

The aim of the study was not to provide a definitive estimate of treatment effect but to try out aspects of the proposed intervention for main trial, so a formal sample size calculation was not conducted. A sample of 30 patients (15 per arm) was deemed large enough to provide useful information about feasibility based on similar pilot studies^{37,92}. The sample was based on the same eligibility criteria that would be used in a future definitive full-scale RCT. It was recognised that the study may not have been powered to detect meaningful differences in clinically important endpoints⁹³.

Statistical analysis

Descriptive data were calculated presenting means and standard deviations for all continuous data and frequencies and percentages for categorical variables at baseline and 3-months' post-randomisation. As this was a pilot study, analysis to determine initial estimates of efficacy for the primary and secondary outcomes was conducted per protocol⁹⁴, comparing intervention Group 1 and control Group 2 only for participants who completed the treatment originally allocated. The difference in mean change between baseline and 3-months follow-up was conducted for the primary (IBD-F) and secondary (IBDQ) outcomes. A power analysis was performed in order to calculate how many patients would have to be included in a potential future trial in order to have 90% power to find a difference at the level of $p = 0.05$ for the fatigue severity subscale of the IBD-F.

Nested qualitative study

Feasibility of delivering the intervention was assessed by conducting semi-structured interviews with the therapists. Both therapists supporting patients during the intervention were interviewed at the end of their intervention delivery. Feasibility of implementation of the intervention within the existing IBD service at the study site was assessed by conducting semi-structured interviews with HCPs working with people with IBD. HCPs in different roles working with people with IBD at the study site were interviewed after recruitment completion.

Acceptability of the intervention to participants was assessed by conducting semi-structured interviews with a sub-set of participants in Group 1. Semi-structured interviews using an Interview Topic Guide were conducted with a sub-set of approximately one-third of participants in Group 1 (CBT + therapist support). The participants were purposively selected to include if possible both genders, a range of ages, both IBD diagnosis and undertaking telephone sessions with both therapists. Furthermore, in the post-intervention follow-up questionnaire all participants in Group 1 were asked about their preferences for the format and delivery, their satisfaction and comments on the intervention.

The nested qualitative study was conducted after the 3-month follow-up quantitative data collection point. Interviews were conducted face to face or over the telephone by a researcher not involved in the delivery of the intervention. Interviews were digitally audio-recorded, anonymised, and transcribed verbatim by a professional transcriber. Two researchers (MA, HP) analysed the data, one of whom (MA) conducted the interviews. Data were analysed using deductive thematic analysis⁹⁵. A pre-existing coding framework was developed utilising the study objectives and the interview schedules in order to answer the specific research questions of the study. Researchers analysed all transcripts independently utilising the same coding framework. Resulting themes were then compared and any differences were resolved by discussion. Themes were then refined prior to producing the final report of key themes and sub themes.

Results

Baseline characteristics

Baseline characteristics of the 31 consent participants are summarised in Table 2.

Table 2: RCT patient participants' baseline characteristics.

Variable, N (%)	Intervention Group 1 (15)	Control Group 2 (16)
Female gender	10 (67)	10 (62)
Age, mean (range), years	37.00 (31)	39.13 (33)
Education		
Up to 16	1 (6.6)	2 (12.5)
Up to 18	0	1 (6.2)
Higher education	14 (93.3)	13 (81.2)
Marital status		
Married/Living with partner	9 (60)	11 (68.7)
Widowed/Divorced	2 (13.3)	0
Single/Single parent/Other	4 (26.7)	5 (31.2)
Employment status		
Full time/Part time	14 (93.3)	13 (81.2)
Retired	0	0
Not working/ Housekeeping	1 (6.6)	3 (18.8)
Living status		
Alone	2 (13.3)	3 (18.8)
With partner/spouse/child/ other relatives/friends	13 (86.7)	13 (81.2)
Smoking status		
Yes	0	1 (6.2)
Ex	5 (33.3)	9 (56.2)
No	10 (66.7)	6 (37.5)
Exercise status (weekly)		
>30 minutes aerobic exercise	12 (80)	10 (62.5)
<30 minutes aerobic exercise	3 (20)	6 (37.5)
Disease classification		
UC	3 (20)	4 (25)
CD	11 (73.4)	10 (62.5)
IBDU	1 (6.6)	2 (12.5)

CD Montreal classification (n= 20)		
L1 ileal	6 (60)	3 (30)
L2 colonic	0	4 (40)
L3 ileocolonic	4 (40)	3 (30)
Months diagnosis, median (range)	171.13 (879)	217.00 (972)
Current medication (Yes)	10 (67)	14 (87)
Thiopurines	6	6
Methotrexate	0	1
Anti-TNF	7	4
Vedolizumab	0	2
Steroids	0	1
Previous IBD surgery (Yes)	1 (25)	4 (25)
Current stoma (Yes)	0	1 (6.2)

Key: anti-TNF- Anti-Tumour Necrosis Factor; CD – Crohn's Disease; IBD- Inflammatory Bowel Disease; IBD-U – Inflammatory Bowel Disease Unclassified; UC – Ulcerative Colitis

There were no significant differences between groups on socio-demographic factors at baseline. There was a significant difference in ESS scores between Group 1 (M= 13.87) and Group 2 (10.19), $p < .040$. No other significant differences between groups at baseline were found.

Feasibility and acceptability outcomes

Recruitment

A total of 89 consecutive patients were referred to the intervention and approached for participation. Seventy of these were eligible and 31 consented to participate, giving a recruitment rate of 44%. A Consort diagram of patient flow is presented in Figure 1. Of the 39 who did not consent for the study, 18 declined to participate and for another 12 contact was lost after initial screening. The main reason for declining to participate was the time commitment required for the study (78%). Other reasons included: hearing problems (11%), currently undergoing other psychological therapy (5.5%) and negative beliefs about CBT (5.5%).

Completeness of outcome data measures

The average percentage of missing data in each completed baseline and 3-months follow-up questionnaire booklet was 3.7%.

Compliance

Patients' post intervention questionnaires (n= 10) indicated 9 (90%) patients read all the sessions of the manual and 8 (80%) completed the homework tasks. Three (30%) of participants spent more than 90 minutes, 2 (20%) spent 60-90 minutes, 5 (50%) spent 30-59 minutes per week completing the intervention.

Retention

Of the 15 participants who consented and were randomised to the intervention group, 13 started the intervention (87%). The therapists' log of patients' sessions indicated that 10 (76.9%) of those who started completed all telephone sessions over 8 weeks. Two (13.3%) discontinued the intervention prior

to commencing the telephone sessions. One participant discontinued due to work schedule interference and one participant due to a newly diagnosed unrelated illness. Three (20%) discontinued the intervention after commencing the telephone sessions. One participant discontinued due to time commitments at Session 1, one due to family illness at Session 2, and one due to perceived un-usefulness of the intervention for their needs at Session 4. Ten (66.7%) participants in intervention Group 1, 12 (75%) in control Group 2 and 22 (71%) participants overall completed baseline and 3-months' follow-up questionnaires.

Acceptability of the interventions: patients' interviews

Post-intervention follow-up survey

The mean satisfaction score from 0-10 (n=10) for intervention Group 1 was 8.6. All participants reported they would continue using the strategies learned in the intervention. Six (60%) participants reported they would complete the intervention online and 4 (40%) participants reported they would have preferred to complete the sessions face-to-face instead of over the telephone.

The mean satisfaction score from 0-10 (n=9) for control Group 2 was 2.4. Participants spent a mean of 9.6 minutes reading the fatigue information sheet. Most of the participants did not find the fatigue information sheet useful as they perceived it did not provide them with any additional strategies to manage fatigue they were not already aware of.

Semi-structured interviews with participants

Of the 15 patients who were randomised to Group 1 of the pilot RCT, 7 were interviewed. Four participants were women and their median age was 40 (range = 19). The majority of participants had CD (n=5), one had UC and one IBD-U. The main themes that emerged from the interviews were: 'Outcomes of the intervention', 'Views on the intervention manual and the telephone sessions', 'Format of the intervention' and 'Suggestions for improvement'. All of the major themes had a few sub themes that were interlinked. The foundations of these themes are described alongside verbatim quotes in *italic*, to illustrate them. Participants are identified in brackets after each quote by using codes for IBD disease type, gender and age.

1. Outcomes of the intervention

i) Impact of the intervention

Feedback on the intervention was mostly positive. Most participants believed that taking part was a worthwhile and valuable experience and that they would recommend it to other people. They reported that the skills they learned positively impacted on their fatigue and their lives to varying degrees. Some participants specifically mentioned feeling disappointed upon completion of the telephone sessions and wishing they would continue for longer.

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'I got quite upset and quite emotional, not upset upset, but emotional about it, because like this has really benefited me and I've really, I really enjoyed doing it and it really benefited me. And I cannot underestimate how, yes, how much it was so useful. I do genuinely feel so much better now' (IBDU_F29)

ii) Useful knowledge/skills acquired with the intervention

As a result of the intervention, participants learned more about fatigue and its causes. They also mentioned specific examples of useful knowledge/skills they acquired which led to improvements in their fatigue and/or quality of life. Almost all participants talked about the negative all-or-nothing behavioural patterns they had been adopting before the trial, and how the intervention had taught them to better pace their activity levels through self-monitoring, introducing breaks, planning their time effectively and learning to say no.

'I would just try and ignore it as best I can and basically get on with it and try and rush and get everything I done before it came to the point I had to stop. Where now I do try and, if you like, pace myself a little bit more. So, it's, I can actually get a little bit more done' (CD_M48)

Participants also often referred to a change in the way they thought and felt about their fatigue, highlighting that having more positive thoughts about fatigue had helped them feel better about it, manage it more effectively and ensure it had a lesser impact on their lives.

'A good part of the study, I found, was trying to focus on different ways to think and I was doing that over a kind of period of it. And it certainly helped' (CD_M44)

Two participants, emphasised how the intervention had aided them to improve their sleep quality, ultimately leading them to have more energy during the day.

'I am getting a better night's sleep. I am having a little bit more energy during the day. I am getting a bit more done...' (CD_F44)

Finally, the same two explained how the intervention had prompted an increase in their physical activity levels.

'I now walk into work now... But I also, in the weekend, I will go for a 40-45-minute walk as well just to – I want to keep on building on it' (IBDU_F29)

2. Views on the intervention manual and the telephone sessions

i) Comprehensibility, structure and completeness of the manual

The information in the manual was perceived to be clear and easy to understand. The content of the manual and the telephone sessions was considered to be well-planned. The manual was thought to be comprehensive and all the topics covered were considered relevant and necessary. Although two participants sometimes found it hard to fit the completion of the homework tasks and one did not find

certain parts of the homework relevant to him, all of the participants acknowledged their importance as enablers to the interventions' positive outcomes.

'I found doing the homework sometimes a little bit of a challenge...but I wouldn't say I wish it wasn't there, because, unless I did it, I wouldn't have got the most out of the process' (CD_F31)

ii) Length, number and intervals between the therapist support sessions

Aside from one participant who thought they were the right length, the majority found the 30-minute telephone sessions to be rushed and would have preferred for them to be longer. One participant suggested merging the two sessions on thoughts and emotions, another recommended the addition of a ninth session that could summarise the content of the intervention, give the opportunity to ask questions and refresh people's memories on the skills they had previously acquired. Not all participants agreed on the intervals between sessions. According to one participant, having sessions once a week worked well because it helped to develop a routine and provide a structure for the completion of the homework tasks. Conversely, the other two participants believed one week in between sessions was not long enough and having two-weekly or monthly sessions would have allowed for more time to reflect on the material and the better identification of behavioural trends through activity monitoring.

3. Format of the intervention

i) Relative importance of the manual versus the telephone sessions

Everyone agreed on the importance of having the manual together with the therapy sessions, as the two complemented each other. The manual provided the participants with useful information they could refer back to in between and after the sessions were completed. Equally, the therapist added to the intervention by explaining the concepts and tailoring examples to participants' needs.

'Until somebody explains what that tool does, it's just words on a page. And that was part of what the therapist was doing, she was explaining why that particular tool, why that particular method would work... So it's not just a process, words on a page, it's something tangible, something that is going to give you a net benefit' (CD_M44)

ii) Modality of communication of the therapy sessions

Responses to the use of the telephone were all positive. The main reported advantage of conducting sessions over the phone was the convenience of not having to travel to the hospital and being able to fit in the sessions during their work day.

iii) Possibility of an online intervention

Views on the possibility of an online intervention were mixed. Participants believed that having the manual in electronic format would be feasible and potentially beneficial for the completion of the homework tasks. However, they recognised the value of having a therapist to support the online

intervention in order to guide the sessions, answer questions and ensure compliance with the intervention.

'Part of what made me really invest in the process was talking to the therapist every week, and having her understand. And having her listen and encourage and support. And you just can't get that from a computer' (CD_M31)

4. Suggestions for improvement

Referring to the intervention manual, participants suggested moving the homework tasks to the end of each corresponding session instead of at the end of the manual, having the option to complete the homework tasks through dictation, adding examples of things other than fatigue where the intervention strategies could be applied, and changing the name of the intervention manual to further emphasise its psychological aspects. In regards to the telephone sessions, participants suggested having someone who had experienced fatigue deliver the intervention and involving a trusted confidant in the last session about social support. Finally, two of the participants, one who dropped out at session 4 and one who completed all eight sessions, advised for a higher threshold of fatigue to be set when enrolling patients in the intervention. Not having experienced negative thoughts associated with fatigue and having already put in place the necessary coping strategies to deal with it, they felt that the intervention was not suitable for them. Conversely, they suggested the intervention may be more useful for people with more severe fatigue or those who have been newly diagnosed and therefore would need to learn strategies to manage the impact of the disease on their lives.

'It would be something that I would have really liked to have had when I was first diagnosed... I'm not sure like now is the right time for me to, for me to have been doing it, because it's, yes, I'm just not in the kind of place, I think, most of the people who are doing this, were' (UC_F31)

Feasibility of delivery: therapists' interviews

Both of the therapists delivering the intervention to Group 1 were interviewed to enquire about their opinions on the feasibility of delivering the intervention. The themes mimicked the ones emerging from patients' interviews.

1. Outcomes of the intervention

The therapists had a very positive experience of delivering the intervention. They believed that there was a need for this type of intervention for patients with IBD-fatigue and that this intervention equipped patients with skills they could apply to self-help in the future. For the therapists the most useful components of the intervention for the patients were: changing the way they thought about fatigue, recognising the importance of the psychological aspects of fatigue, realising that they were not alone in their suffering from fatigue and learning to monitor and schedule their activities more effectively.

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'Towards the end, whether knowingly or not, I don't know, they would start, you could see that kind of their perspectives had changed slightly. And they'd start rephrasing things or talking about things in a slightly different way without being prompted' (Therapist1)

Although according to one therapist the intervention could also be adapted for a more moderate severity, both therapists thought that the intervention was more appropriate for patients who experienced more severe levels of fatigue. Furthermore, one therapist stressed the importance of offering the therapy only to patients seeking help for fatigue and the other suggested it could benefit patients at the point of diagnosis.

'If people are afflicted with the fatigue and it has an impact, they're potentially more motivated than someone who maybe isn't experiencing the fatigue as badly' (Therapist1)

2. Views on the intervention manual and the telephone sessions

The manual was perceived to be a good resource for the therapists and the patients. Whilst one therapist found the colour coding of the pages of the sessions useful, the other found it off-putting and would have preferred the use of coloured index tabs. Both therapists also suggested to move the homework tasks at the end each session, instead of having a homework booklet at the end of the manual. Additionally, one therapist advised it would be beneficial for patients' to continue their activity monitoring for 2 weeks instead of only for one week.

The therapists agreed that the 30-minutes sessions were too short and would have preferred the sessions to be at least 45 minutes. Whilst one therapist considered the number of sessions to be appropriate, the other would have preferred to add an additional ninth session on thoughts. Moreover, it was suggested either switching the order of the sessions to bring the one on thoughts forward or having the option to keep the order of the sessions flexible so it could be tailored to patients' needs.

3. Format of the intervention

Although the therapists were initially concerned about not being able to pick-up non-verbal cues over the phone, they both agreed that anonymity of the phone may have ultimately allowed patients to self-disclose more than if the sessions had been face-to-face. However, one therapist suggested that face-to-face sessions would have pushed some patients to get out of bed and the other believed that having the first session face-to-face could have made patients more vested in the process.

'I think it was – it normalised it nearly, because you have phone conversations all the time' (Therapist1)

There was disagreement on the relative importance of the manual and the therapists' sessions. One therapist thought that the manual could be utilised by patients on their own and that they might only struggle on more complex topics such as 'thought-challenging'. The other was adamant that a therapist was necessary to guide them through the sessions.

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'They need to have access to somebody who's going to coach them through it' (Therapist2)

Both therapists agreed that although no prior experience with IBD patients was needed to deliver the intervention, it would have been useful to have a better knowledge of the physical symptoms experienced by patients with IBD and the medications utilised for its management. According to one therapist, a CBT therapist with experience in fatigue would be the ideal HCP to deliver the intervention yet an IBD-nurse specialist could potentially deliver it with adequate CBT training.

'I think they would nearly be more, I don't want to say 'qualified', that's the wrong term, but in a better place to deliver it with some training about kind of CBT techniques and Socratic questioning and all those kind of things, than potentially a CBT therapist or a clinical psychologist who had very, very little experience of IBD' (Therapist1)

Taking into account barriers such as computer illiteracy and difficulty in accessing the online information once the intervention has ended, one therapist believed that an online intervention could be beneficial in providing a more tailored experience for the patients.

4. Suggestions for improvement

The therapists advised other suggestions for improvement of the intervention, including: adding more real-life examples in the manual, utilising the term 'home practice' instead of 'homework', having an online booking system for appointments, sending photos of the homework tasks to the therapist through a secure transfer method and organising the opportunity for patients with IBD-fatigue to share their experiences between them (online and/or in person).

Feasibility of implementation: HCPs' interviews

Four HCP (one consultant gastroenterologist [CG], one IBD-nurse specialist [CNS] and two IBD research fellows [RF]) were interviewed to enquire about their opinions on the feasibility of implementing the intervention in their IBD service. The main themes that emerged from the interviews were: 'Benefits of the intervention' and 'Barriers to the intervention'.

1. Benefits of the intervention

Although doctors reported routinely enquiring about other IBD-related symptoms, they reported only discussing fatigue if the patient brought it up. Indeed, both doctors and the nurse acknowledged that having a conversation about fatigue may add time to the consultation, making it difficult to find the time to talk about it in detail. Indeed, all HCPs reported struggling to help patients with the understanding and management of fatigue and wanting to offer patients a solution for their fatigue. Furthermore, the need for a psychological support service for IBD patients was expressed. HCPs felt that if a psychologist was employed to deliver the fatigue management intervention they could also support patients for other psychological problems which are not currently addressed by the service.

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'As clinicians, it would be a good way of solving a problem that currently we can't solve, or, at least offering a possible solution, because we don't have much to offer them' (CG01)

HCPs found the intervention to be comprehensive and useful, and they appreciated its structure in separate sections. They thought the applicability of the intervention was quite broad. One doctor reported initially being sceptical about patients' response to the intervention, yet he subsequently found patients to be keen to be involved.

'I think my first thought was that patients are going to go, "Well I'm not making it up, if you think I'm making it up." But they haven't actually. They're very keen on it and they're very keen to be involved. And they thought it was a very good idea' (RF02)

Likewise, another doctor reported recruitment for the intervention to be straightforward. Two HCPs agreed they would offer the intervention to anyone in remission. Additionally, the nurse suggested that certain aspects of the intervention may benefit also patients with active disease.

2. Barriers to the intervention

Time, training and financial resources were found to be barriers to the implementation of the intervention. All HCPs reported time being a barrier. The four and a half hours of one-on-one time needed for the telephone sessions were recognised as a significant amount of time if the number of patients interested in the intervention was expected to grow. Both doctors and the nurse acknowledged that the nurses would not have the time to deliver the intervention and that if they made the time, other aspects of the service would suffer. Likewise, no one else in the current team was seen as having the time to offer the intervention to all IBD-patients suffering from fatigue.

'There is no way that our nursing service could take on that burden' (CG01)

HCPs all agreed that an additional HCP would therefore have to be employed specifically to oversee the intervention. Alternatively, either the intervention manual would have to be given to patients without the support sessions or an internet platform/app would have to be designed for the patients to self-manage their fatigue.

'If there's an internet platform or an app of some description that they could do the necessary exercises and take them through the process without needing someone else to guide them, that would be, you know, that would be ideal' (RF03)

The nurse believed that the nurses would benefit from having adequate training on IBD-fatigue management. However, she did not have a clear idea of what the training would look like. Lastly, all the doctors acknowledged the need for taking the cost of the one-on-one support sessions and funding into account when considering the implementation of the intervention. The doctors suggested different ways in which cost-effectiveness of the intervention could be proven. One interviewee suggested that addressing fatigue and other psychological problems may in turn improve IBD and save money in the

long-run. More specifically, the consultant argued that cost-effectiveness could be assessed and shown through reductions in outpatient appointments in a trial.

'There may be an argument, you know, with certain patients, tackling their fatigue or whatever other psychological problems they may have. You may be able to intervene and get them medically better, which may save money in the long term' (RF01)

Initial estimates of efficacy outcomes

Table 3 shows means and standard deviations for outcome measures at baseline and 3-months post-randomisation by treatment group.

Table 3: Means and standard deviations of outcome measures of participants who completed baseline and 3-months follow-up measures.

Outcome	Group	Baseline			3-months follow-up		
		Mean	SD	N	Mean	SD	N
HBI	Group 1	3.30	3.20	10	5.50	6.05	8
	Group 2	4.33	2.74	9	5.50	4.46	6
SCCAI	Group 1	5.22	3.22	3	4.00	2.83	2
	Group 2	4.50	2.52	4	4.50	1.22	6
IBD-F severity	Group 1	11.93	3.24	14	8.00	4.61	9
	Group 2	9.93	4.13	15	9.45	4.97	11
IBD-F impact	Group 1	55.83	26.74	12	23.40	15.09	10
	Group 2	49.00	28.66	15	44.20	30.96	10
IBDQ	Group 1	89.67	13.67	15	97.50	11.20	10
	Group 2	93.79	8.87	14	95.27	10.10	11
BIPQ	Group 1	41.13	6.20	15	32.40	6.83	10
	Group 2	42.40	7.14	15	43.20	6.14	10
ESS	Group 1	13.87	4.85	15	7.00	4.42	10
	Group 2	10.19	4.69	16	9.82	3.90	11
GAD7	Group 1	9.80	5.54	15	4.50	3.53	10
	Group 2	8.00	5.27	16	5.00	3.52	11
PHQ9	Group 1	12.00	6.01	15	6.00	4.42	10

Group 2	9.75	6.00	16	8.73	4.71	11
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Key: **BIPO** – Brief Illness Perceptions Questionnaire; **ESS** – Epworth Sleepiness Scale; **GAD** – Generalized Anxiety Disorder; **HBI**; Harvey Bradshaw Index; **IBD-F**; Inflammatory Bowel Disease-Fatigue; **IBDQ**; Inflammatory Bowel Disease Questionnaire; **PHQ** – Patient Health Questionnaire; **SCCAI**; Simple Clinical Colitis Activity Index; **SD**; Standard Deviation

Table 4 shows means, standard deviations and change scores of those who completed the primary and secondary outcomes at baseline and 3-months post-randomisation. There was a reduction in IBD-F fatigue severity and fatigue impact in scores in both groups. Participants in Group 1 showed a mean change score of -4.29 (SD = -5.28) at 3-months compared to baseline for fatigue severity. Participants in Group 2 showed a mean change score of -1.18 (SD= -2.68) at 3-months compared to baseline. The mean difference between the change scores in Group 1 and Group 2 (mean difference [MD] = -3.10, CI= -7.10, $p = 0.86$) was not significant. Participants in Group 1 showed a mean change score of -31.00 (SD = -25.72) at 3-months compared to baseline for fatigue impact. Participants in Group 2 showed a mean change score of -4.11 (SD= -20.08) at 3-months compared to baseline. There was a significant difference in the change scores in Group 1 and Group 2 (MD = -26.89, CI= -51.39, -2.39, $p = .034$).

There was an improvement in IBDQ quality of life in both groups. Participants in Group 1 showed a mean change score of 7.33 (SD = 11.56) at 3-months compared to baseline. Participants in Group 2 showed a mean change score of 4.00 (SD = 8.02) at 3-months compared to baseline. The mean difference between the change scores in Group 1 and Group 2 (MD = 3.33, CI=-6.21, 12.88) was not significant.

Table 4: Means, standard deviations and change scores for the primary and secondary outcomes of participants who completed baseline and 3-months follow-up measures and the CBT and control interventions per protocol.

Outcome	Group	Baseline		3-months follow-up			Change Scores		
		Mean	SD	Mean	SD	N	Mean	SD	MD (CI)
IBDF-1	Group 1	11.57	3.60	7.29	3.95	7	-4.29	-5.28	-3.10 (-7.10, 0.86)
	Group 2	10.64	4.25	9.45	4.55	11	-1.18	-2.68	
IBDF-2	Group 1	56.71	32.53	25.71	15.64	7	0	-25.72	-26.89 (-51.39, -2.39)*
	Group 2	51.44	33.23	47.33	31.12	9	-4.11	-20.08	
IBDQ	Group 1	87.60	13.64	95.89	10.58	9	7.33	11.56	3.33 (-6.21, 12.88)
	Group 2	91.70	9.80	95.70	10.54	10	4.00	8.04	

* $p < .005$

Key: **CI**- Confidence Interval; **MD**- mean difference; **SD**- Standard Deviation

Sample size calculation

To detect a mean difference in IBD-F severity scores at 12-months post-randomisation with a two-sided significance level of 5% and a power of 90% with equal allocation to two arms would require 61 participants in each arm of the trial. To allow for a drop-out of approximately 29% (finding from this study) at 3-months post-randomisation and a 10% drop-out at both 6 and 12-months post-randomisation, then a minimum of 107 IBD patients should be recruited per arm (214 in total).

Discussion

This pilot study aimed to evaluate the feasibility and initial estimates of efficacy of a CBT intervention for fatigue in patients with IBD. Quantitative and qualitative methods were utilised to determine whether the progression criteria for continuation to a full-scale effectiveness trial were met. Feasibility progression criteria assessing completeness of outcome measures and compliance were met, those of recruitment and retention were not fully achieved. The intervention was acceptable to patients and feasible for the CBT therapists to deliver. However, HCPs identified potential barriers to the feasibility of implementation of the intervention. There were greater improvements at 3-months post-randomisation in severity and impact of fatigue and QoL for intervention Group 1 compared to control Group 2, yet these differences were significant only for impact of fatigue. Preliminary efficacy analysis from the study thus indicates that changing patients' feelings, cognitions and behaviours in relation to fatigue may improve the impact that fatigue has on their lives. Overall these findings suggest a full-scale effectiveness RCT testing CBT for IBD-fatigue is feasible and has a potential for improvement of fatigue with some changes to the protocol. The advised revisions are discussed below.

Feasibility and acceptability outcomes

The questionnaires returned by participants had an average of 3.7% missing item responses suggesting that the measures used were acceptable to patients⁹⁶. The use of mobile apps for questionnaire completion in the full-scale trial could nonetheless further improve data completeness compared to using paper questionnaires⁹⁷. Ninety percent of participants were compliant by reading all the sessions in the manual and all of them reported spending more than 15 minutes per week performing the intervention tasks. Furthermore, although 13% of participants randomised to intervention Group 1 did not start the therapist support sessions, 77% of those who started completed all 8. Compared to the original intervention for MS-fatigue⁷¹ where all participants completed 100% of the sessions, this may suggest first treatment exposure to be a central treatment component of CBT⁹⁸. Indeed, having completed at least one session versus to not having completed any sessions is a strong predictor of engagement and long-term symptom reduction in CBT trials. Including strategies to improve engagement at the beginning of the intervention may therefore be an key feature to incorporate in the full-scale trial⁹⁹. Telephone sessions, which were very positively received by the participants, may also have contributed to the high compliance rates. Telephone delivery can reduce the geographical barriers

associated with face-to-face therapy¹⁰⁰ and more interestingly it may overcome patient ambivalence towards psychological treatment¹⁰¹, ultimately reducing attrition¹⁰². The inclusion of telephone sessions should thus be included in the full-scale trial.

Although recruitment target for participants was achieved, 44% of eligible participants consented for participation instead of 50% as defined a-priori. The main reason for declining to participate was the time commitment required for the intervention, indicating time required from patients may be a potential barrier to the uptake of a full-scale CBT trial¹⁰³. Online intervention modalities which increase flexibility for patients in regard to time and location of accessing treatment¹⁰⁴, should thus be considered to incentivise participation. Conversely, as lack of motivation to take part has been posited as a reason for drop-out from trials¹⁰⁵, it is nevertheless important to recruit those patients who are motivated to participate in the CBT trial because their fatigue is burdensome. Findings from our interviews showed that HCPs rarely ask about fatigue and not all patients mention it during outpatient consultations, making recruitment of patients experiencing fatigue through clinician referral difficult. Integrating an observational screening phase into the full-scale RCT where patients who need and want fatigue management are identified, may hence be beneficial to increase recruitment rates.

The withdrawal rate during treatment of 23% and reasons for withdrawal are comparable to meta-analytic findings on CBT drop-out rates across conditions¹⁰⁶. Nonetheless, withdrawal rates were slightly higher than the 20% initially anticipated for progression to the full-scale RCT. Likewise, 4 out of the 16 participants in control Group 2 and 5 out of the 15 patients in intervention Group 1 did not return the completed questionnaires despite the two reminders. One possible reason for these higher than expected loss to follow-up rates may be associated with participants' perception of subjective benefits as a result of the intervention. When participants perceive that they have experienced positive changes they may be more motivated to comply with the trial procedures¹⁰⁷. Conversely for participants who have withdrawn from the support sessions or those have been randomised to the control group may be less invested in returning the follow-up questionnaires¹⁰⁸. Unfortunately, blinding of participants is impossible in psychosocial interventions¹⁰⁹. However, using a trial design for the full-scale RCT which includes a comparison instead of a control group and in which intervention time is kept constant across the two groups may help to minimise the effect of patients' expectancy on attrition¹¹⁰.

Most participants in intervention Group 1 provided positive opinions regarding an acceptably positive experience of taking part in the intervention. Participants believed that the intervention manual complemented the therapist support sessions and they reported changes in patterns of negative feelings, cognitions and emotions in line with the CBT aims. The therapists reported that they would use this intervention for the management of IBD-fatigue so as to equip patients with skills to self-help. However, both the patients and CBT therapists agreed that the intervention was more useful for patients with higher fatigue levels. Assessment of higher levels of fatigue utilising standardised fatigue measures should therefore be included when screening for eligibility in the full-scale RCT. Additional changes

suggested by the participants and CBT therapists to improve feasibility and acceptability of the intervention included: increasing the length of the telephone sessions, having the homework tasks at the end of each corresponding session, using an online-booking system to book appointments and sending photos of homework tasks to the therapists to ensure compliance. These suggestions should feed into future intervention development.

Despite HCPs finding a broad applicability and perceived utility of the intervention to their IBD patient group, they identified potential time, training and financial barriers to the feasibility of implementation of the intervention within their current IBD service. No current member of their IBD team was seen to have enough time and adequate training to deliver the intervention. The presence of an economic evaluation of the intervention to demonstrate its cost-effectiveness is consequently important in the full-scale RCT. Additionally, considering online interventions with therapist support sessions may have the potential to reduce demand on clinicians and lower costs whilst still maintaining a personalised approach to patients and controlling attrition¹¹¹. Indeed, as CBT manuals are characterised by being systematic and operationalised¹¹² they can translate well into computerised interventions¹¹³. Likewise, while tailoring therapy to individual needs is more resource intensive up front, it might yield better outcomes over time than entirely self-directed online therapies⁶⁶.

Strengths and limitations

Development of the intervention was guided by the MRC framework for complex interventions⁷⁵, based on cognitive-behavioural theory and empirical evidence in IBD and other long-term conditions. Extensive consultation with patients was conducted in order to make the intervention more relevant and acceptable to the target population. Nonetheless, analysis of pilot studies should be mainly descriptive resulting in preliminary findings which should be tested in large-scale effectiveness RCTs¹¹⁴. The sample was limited to patients attending one tertiary referral centre and cannot therefore be generalised to the wider population of IBD patients. The use of patient self-report DAI scores may have resulted in incomplete or inaccurate data on remission status. Although self-reported DAIs are often utilised in research studies, it is best practice for clinicians to complete them after obtaining information from patients¹¹⁵ and/or use calprotectin or endoscopic assessments¹¹⁶. In addition, the interviews were conducted by one of the investigators involved in recruitment of patients, which may have influenced the extent to which participants were willing to be critical. Lastly, the per protocol analysis could have potentially affected the external validity of the trial, as those who persevere with treatment per protocol represent a non-random sample of the original group of participants¹¹⁷. It cannot be expected that participants who do not use materials will gain benefits from the intervention, so the per protocol analysis is justified in this context. Efforts should nonetheless focus on increasing treatment compliance in interventions to avoid bias⁶⁸.

Conclusions

Despite the limitations, this pilot study makes a unique contribution to the body of knowledge on feasible and effective treatments for the management of IBD-fatigue. This is the first intervention to test the applicability of CBT treatment models for fatigue with proven effectiveness in other long-term conditions to patients with IBD. The preliminary findings showing a significant improvement in impact of fatigue on daily activities in intervention Group 1 compared to control Group 2 indicate a potential for improvement of IBD-fatigue utilising CBT. A large-scale effectiveness RCT is now needed to investigate maintenance of treatment gains and the cost-effectiveness of the therapy. Incorporating changes to the protocol and an online intervention may ultimately be an effective way to overcome the barriers to implementation identified by HCPs and test the generalisability of the intervention to IBD-clinical practice.

List of abbreviations

CBT	Cognitive Behavioural Therapy
CCUK	Crohn's and Colitis UK
CD	Crohn's Disease
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive Protein
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Healthcare Professional
MRC	Medical Research Council
NIHR	National Institute of Healthcare Research
NRES	National Research Ethics Service
IBD	Inflammatory Bowel Disease
MS	Multiple Sclerosis
NHS	National Health Service
PPI	Patient Public Involvement

PRO	Patient Reported Outcome
QOL	Quality of Life
RCT	Randomised Controlled Trial
RT	Relaxation Therapy
REC	Research Ethics Committee
SFT	Solution Focused Therapy
UC	Ulcerative Colitis
UK	United Kingdom

Declarations

Ethics approval and consent to participate

The study was granted ethical approval by the United Kingdom National Research Ethics Service - North West - Liverpool Central Committee (16/NW/0791). Eligible patients were provided with a Patient Information Sheet explaining the nature and the aims of the study. Patients had the opportunity to fully consider their participation in the study for at least 48 hours. Signed informed consent were returned with the baseline questionnaires by post. All participants were allocated a study number to protect their anonymity.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated or analysed during the current study are not publicly available [individual privacy of the participants could be compromised] but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was part of a PhD project funded by King's College London.

Authors' contributions

MA, WCD, CN, JS were responsible for the conception of the study; MA conducted the organisation of the study; MA and HP conducted the analysis; MA was responsible for the drafting the manuscript. All authors have read and commented on the final version of this article and are responsible for its content.

Acknowledgements

We thank the IBD team at the hospital site where we recruited, the Patient and Public Involvement group and the patient participants who took part in the study. We also acknowledge the therapists who delivered the intervention and the students Sylwia Kubasiewicz and Eve Didymus who helped us with the interview analysis.

References

1. Siegel CA, Whitman CB, Spiegel BMR, et al. Development of an index to define overall disease severity in IBD. *Gut* 2016;Published Online First: 25 October 2016. doi: 10.1136/gutjnl-2016-312648.
2. Baumgart DC, Sandborn WJ. Crohn's disease. *The Lancet* 2016;380(9853):1590-1605.
3. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. *The Lancet* 2016;389(10080):1756-1770.
4. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *Journal of Crohn's and Colitis* 2012;6(10):965-990.
5. Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *Journal of Crohn's and Colitis* 2016;11(1):3-25.
6. Bardhan K, Simmonds N, Royston C, Dhar A, Edwards C. A United Kingdom inflammatory bowel disease database: making the effort worthwhile. *Journal of Crohn's and Colitis* 2010;4(4):405-412.
7. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. *Scandinavian journal of gastroenterology* 2015;50(8):942-951.
8. O'Connor M, Bager P, Duncan J, et al. N-ECCO Consensus statements on the European nursing roles in caring for patients with Crohn's disease or ulcerative colitis. *Journal of Crohn's and Colitis* 2013;7(9):744-764.
9. Peyrin-Biroulet L, Sandborn W, Sands B, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *The American journal of gastroenterology* 2015;110(9):1324-1338.
10. Williet N, Sarter H, Gower-Rousseau C, et al. Patient reported-outcomes in a French nationwide survey of inflammatory bowel disease patients. *Journal of Crohn's and Colitis* 2016.
11. Schoultz M, Macaden L, Watson AJM. Co-designing inflammatory bowel disease (Ibd) services in Scotland: findings from a nationwide survey. *BMC Health Services Research* 2016;16(1):231.
12. Casellas F, Herrera-de Guise C, Robles V, Navarro E, Borruel N. Patient preferences for inflammatory bowel disease treatment objectives. *Digestive and Liver Disease* 2016.
13. Czuber-Dochan W, Dibley LB, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: an exploratory study. *Journal of Advanced Nursing* 2013;69(9):1987-1999.
14. Matini L, Ogden J. A qualitative study of patients' experience of living with inflammatory bowel disease: A preliminary focus on the notion of adaptation. *Journal of Health Psychology* 2016;21(11):2493-2502.
15. Lönnfors S, Vermeire S, Avedano L. IBD and health-related quality of life—discovering the true impact. *Journal of Crohn's and Colitis* 2014;8(10):1281-1286.
16. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue; A practical guide for clinicians and researchers. *J Psychosom Res* 2004;56.
17. van Langenberg DR, Gibson PR. Factors associated with physical and cognitive fatigue in patients with Crohn's disease: a cross-sectional and longitudinal study. *Inflammatory bowel diseases* 2014;20(1):115-125.

18. Wilburn J, Twiss J, Kemp K, McKenna SP. A qualitative study of the impact of Crohn's disease from a patient's perspective. *Frontline Gastroenterology* 2017;**8**(1):68-73.
19. Woodward S, Dibley L, Coombes S, et al. Identifying disease-specific distress in patients with inflammatory bowel disease. *Br J Nurs* 2016;**25**:649-60.
20. Pittet V, Vaucher C, Froehlich F, et al. Patient self-reported concerns in inflammatory bowel diseases: A gender-specific subjective quality-of-life indicator. *PloS one* 2017;**12**(2):e0171864.
21. Hart AL, Lomer M, Verjee A, et al. What are the top 10 research questions in the treatment of inflammatory bowel disease? A Priority Setting Partnership with the James Lind Alliance. *Journal of Crohn's and Colitis* 2016;jjw144.
22. Dibley L, Bager P, Czuber-Dochan W, et al. Identification of Research Priorities for Inflammatory Bowel Disease Nursing in Europe: a Nurses-European Crohn's and Colitis Organisation Delphi Survey. *Journal of Crohn's and Colitis* 2017;**11**(3):353-359.
23. Van Langenberg D, Gibson P. Systematic review: fatigue in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2010;**32**(2):131-143.
24. Czuber-Dochan W, Norton C, Bredin F, Darvell M, Nathan I, Terry H. Healthcare professionals' perceptions of fatigue experienced by people with IBD. *Journal of Crohn's and Colitis* 2014;**8**(8):835-844.
25. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflammatory bowel diseases* 2011;**17**(7):1564-1572.
26. Tew GA, Jones K, Mikocka-Walus A. Physical activity habits, limitations, and predictors in people with inflammatory bowel disease: a large cross-sectional online survey. *Inflammatory bowel diseases* 2016;**22**(12):2933-2942.
27. Norton C, Czuber-Dochan W, Bassett P, et al. Assessing fatigue in inflammatory bowel disease: comparison of three fatigue scales. *Alimentary Pharmacology & Therapeutics* 2015;**42**(2):203-211.
28. Bager P, Befrits R, Wikman O, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Alimentary pharmacology & therapeutics* 2012;**35**(1):133-141.
29. Yoo S, Jung YS, Park JH, et al. Fatigue severity and factors associated with high fatigue levels in Korean patients with inflammatory bowel disease. *Gut and liver* 2014;**8**(2):148.
30. Banovic I, Gilibert D, Jebrane A, Cosnes J. Diagnostic profiles determined by the CART procedure: IBD patients and fatigue. *Journal of health psychology* 2011;1359105311419268.
31. Cohen B, Zoëga H, Shah S, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Alimentary pharmacology & therapeutics* 2014;**39**(8):811-822.
32. Artom M, Czuber-Dochan W, Sturt J, Murrells T, Norton C. The contribution of clinical and psychosocial factors to fatigue in 182 patients with inflammatory bowel disease: a cross-sectional study. *Alimentary pharmacology & therapeutics* 2017;**45**(3):403-416.
33. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflammatory bowel diseases* 2011;**17**(9):1882-1889.
34. Graff LA, Clara I, Walker JR, et al. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clinical Gastroenterology and Hepatology* 2013;**11**(9):1140-1146.
35. Hashash J, Ramos-Rivers C, Youk A, et al. Quality of Sleep and Coexistent Psychopathology Have Significant Impact on Fatigue Burden in Patients With Inflammatory Bowel Disease. *Journal of clinical gastroenterology* 2016.

36. Grimstad T, Norheim KB, Isaksen K, et al. Fatigue in newly diagnosed inflammatory bowel disease. *Journal of Crohn's and Colitis* 2015;**9**(9):725-730.
37. Vogelaar L, van't Spijker A, Vogelaar T, et al. Solution focused therapy: A promising new tool in the management of fatigue in Crohn's disease patients: Psychological interventions for the management of fatigue in Crohn's disease. *Journal of Crohn's and Colitis* 2011;**5**(6):585-591.
38. Vogelaar L, van't Spijker A, Timman R, et al. Fatigue management in patients with IBD: a randomised controlled trial. *Gut* 2014;**63**(6):911-918.
39. McNelly AS, Nathan I, Monti M, et al. A randomised controlled pilot study investigating the effect of increasing physical activity and/or omega-3 supplementation on fatigue in patients with inflammatory bowel disease. *Gastrointestinal Nursing* 2016.
40. Costantini A, Pala MI. Thiamine and fatigue in inflammatory bowel diseases: an open-label pilot study. *The Journal of Alternative and Complementary Medicine* 2013;**19**(8):704-708.
41. Szigethy E, McAuliff K, Strassburger M, et al. 6.20 BRIEF BEHAVIORAL THERAPY AND BUPROPION FOR SLEEP AND FATIGUE IN ADOLESCENTS AND YOUNG ADULTS WITH INFLAMMATORY BOWEL DISEASE. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016;**55**(10):S210.
42. Loftus EV, Feagan BG, Colombel J-F, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *The American journal of gastroenterology* 2008;**103**(12):3132-3141.
43. Lichtenstein GR, Bala M, Han C, DeWoody K, Schaible T. Infliximab improves quality of life in patients with Crohn's disease. *Inflammatory bowel diseases* 2002;**8**(4):237-243.
44. Minderhoud IM, Samsom M, Oldenburg B. Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? *World journal of gastroenterology: WJG* 2007;**13**(14):2089-2093.
45. Hetzel D, Strauss W, Bernard K, Li Z, Urboniene A, Allen LF. A Phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy. *American journal of hematology* 2014;**89**(6):646-650.
46. Grimstad T, Norheim KB, Kvaløy JT, et al. Conventional treatment regimens for ulcerative colitis alleviate fatigue – an observational cohort study. *Scandinavian Journal of Gastroenterology* 2016:1-7.
47. Garcia-Vega E, Fernandez-Rodriguez C. A stress management programme for Crohn's disease. *Behaviour research and therapy* 2004;**42**(4):367-383.
48. Szigethy E, McAuliff K, Strassburger M, et al. 6.20 BRIEF BEHAVIORAL THERAPY AND BUPROPION FOR SLEEP AND FATIGUE IN ADOLESCENTS AND YOUNG ADULTS WITH INFLAMMATORY BOWEL DISEASE. *Journal of the American Academy of Child & Adolescent Psychiatry*; **55**(10):S210.
49. Czubor-Dochan W. Exploring fatigue in inflammatory bowel disease as experienced by individuals - a descriptive phenomenological study: King's College London; 2015.
50. Artom M, Czubor-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. *Journal of Crohn's and Colitis* 2016.
51. Hackett KL, Lambson RL, Strassheim V, Gotts Z, Deary V, Newton JL. A concept mapping study evaluating the UK's first NHS generic fatigue clinic. *Health Expectations* 2016;**19**(5):1138-1149.
52. Lippke S, Ziegelmann JP. Theory-based health behavior change: Developing, testing, and applying theories for evidence-based interventions. *Applied Psychology* 2008;**57**(4):698-716.

53. Van Kessel K, Moss-Morris R. Understanding multiple sclerosis fatigue: a synthesis of biological and psychological factors. *Journal of psychosomatic research* 2006;**61**(5):583-585.
54. Deary V, Chalder T, Sharpe M. The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. *Clinical psychology review* 2007;**27**(7):781-797.
55. Hewlett S, Ambler N, Almeida C, et al. Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. *Annals of the rheumatic diseases* 2011;**70**(6):1060-1067.
56. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognitive Therapy and Research* 2012;**36**(5):427-440.
57. Thomas PW, Thomas S, Kersten P, et al. Multi-centre parallel arm randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based cognitive behavioural approach to managing fatigue in people with multiple sclerosis. *BMC neurology* 2010;**10**(1):1.
58. von Wietersheim J, Kessler H. Psychotherapy with chronic inflammatory bowel disease patients: a review. *Inflammatory bowel diseases* 2006;**12**(12):1175-1184.
59. Goodhand JR, Wahed M, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? *Expert review of gastroenterology & hepatology* 2009;**3**(6):661-679.
60. Timmer A, Preiss JC, Motschall E, Rücker G, Jantschek G, Moser G. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev* 2011;**2**.
61. Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. *Inflammatory bowel diseases* 2013;**19**(12):2704-2715.
62. McCombie AM, Mulder RT, Geary RB. Psychotherapy for inflammatory bowel disease: a review and update. *Journal of Crohn's and Colitis* 2013;**7**(12):935-949.
63. Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology* 2017;**2**(3):189-199.
64. Wahed M, Corser M, Goodhand JR, Rampton DS. Does psychological counseling alter the natural history of inflammatory bowel disease? *Inflammatory bowel diseases* 2010;**16**(4):664-669.
65. Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. *BMC gastroenterology* 2015;**15**(1):54.
66. Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. *International Journal of Behavioral Medicine* 2017;**24**(1):127-135.
67. Keefer L, Doerfler B, Artz C. Optimizing Management of Crohn's Disease Within a Project Management Framework: Results of A Pilot Study. *Inflammatory Bowel Diseases* 2012;**18**(2):254-260.
68. McCombie A, Geary R, Andrews J, Mulder R, Mikocka-Walus A. Does computerized cognitive behavioral therapy help people with inflammatory bowel disease? A randomized controlled trial. *Inflammatory bowel diseases* 2016;**22**(1):171-181.
69. Skerrett TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms. *Journal of psychosomatic research* 2006;**61**(5):587-593.

70. Jordan C, Ohlsen R, Hayee BH, Chalder T. A qualitative study exploring the experience of people with IBD and elevated symptoms of anxiety and low mood and the type of psychological help they would like. *Psychology & Health* 2017;1-18.
71. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosomatic Medicine* 2008;70(2):205-213.
72. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. *Behaviour research and therapy* 2012;50(6):415-421.
73. Leventhal H, Meyer D, Nerenz D. The common sense representation of illness danger. *Contributions to medical psychology* 1980;2:7-30.
74. Knoop H, Van Kessel K, Moss-Morris R. Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychological medicine* 2012;42(01):205-213.
75. Craig P, Dieppe P, Macintyre S. Developing and evaluating complex interventions: the new medical research council guidance. *Br Med J*. 2008;337.
76. Czuber-Dochan W, Ream E, Norton C. Review article: description and management of fatigue in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics* 2013;37(5):505-516.
77. McCombie A, Gearry R, Mulder R. Preferences of inflammatory bowel disease patients for computerised versus face-to-face psychological interventions. *Journal of Crohn's and Colitis* 2014;8(6):536-542.
78. Muller I, Yardley L. Telephone-delivered cognitive behavioural therapy: a systematic review and meta-analysis. *Journal of Telemedicine and Telecare* 2011;17(4):177-184.
79. Artom M, Czuber-Dochan W, Sturt J, Norton C. Cognitive behavioural therapy for the management of inflammatory bowel disease-fatigue with a nested qualitative element: study protocol for a randomised controlled trial. *Trials* 2017;18(1):213.
80. Wilson GT, Wilfley DE, Agras WS, Bryson SW. Allegiance Bias and Therapist Effects: Results of a Randomized Controlled Trial of Binge Eating Disorder. *Clinical psychology : a publication of the Division of Clinical Psychology of the American Psychological Association* 2011;18(2):119-125.
81. Midgley N, Ansaldo F, Target M. The meaningful assessment of therapy outcomes: Incorporating a qualitative study into a randomized controlled trial evaluating the treatment of adolescent depression. *Psychotherapy* 2014;51(1):128.
82. Hill CE, Knox S, Thompson BJ, Williams EN, Hess SA, Ladany N. Consensual qualitative research: An update. *Journal of counseling psychology* 2005;52(2):196.
83. Williams EN, Morrow SL. Achieving trustworthiness in qualitative research: A pan-paradigmatic perspective. *Psychotherapy Research* 2009;19(4-5):576-582.
84. Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *J Crohns Colitis* 2014;8.
85. Cheung WY, Garratt AM, Russell IT, Williams JG. The UK IBDQ—a British version of the inflammatory bowel disease questionnaire: development and validation. *J Clin Epidemiol* 2000;53.
86. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *Journal of psychosomatic research* 2006;60(6):631-637.
87. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *sleep* 1991;14(6):540-545.

88. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine* 2006;**166**(10):1092-1097.
89. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;**16**.
90. Harvey R, Bradshaw J. A simple index of Crohn's-disease activity. *The Lancet* 1980;**315**(8167):514.
91. Walmsley R, Ayres R, Pounder R, Allan R. A simple clinical colitis activity index. *Gut* 1998;**43**(1):29-32.
92. Schoultz M, Atherton I, Watson A. Mindfulness-based cognitive therapy for inflammatory bowel disease patients: findings from an exploratory pilot randomised controlled trial. *Trials* 2015;**16**(1):379.
93. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC medical research methodology* 2010;**10**(1):1.
94. Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. *Physical therapy reviews* 2009;**14**(1):36-49.
95. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;**3**.
96. Brédart A, Razavi D, Robertson C, et al. Timing of patient satisfaction assessment: effect on questionnaire acceptability, completeness of data, reliability and variability of scores. *Patient Education and Counseling* 2002;**46**(2):131-136.
97. Marcano BJ, Jamsek J, Huckvale K, O'Donoghue J, Morrison C, Car J. Comparison of self-administered survey questionnaire responses collected using mobile apps versus other methods. *The Cochrane database of systematic reviews* 2015(7):MR000042.
98. Longmore RJ, Worrell M. Do we need to challenge thoughts in cognitive behavior therapy? *Clin Psychol Rev* 2007;**27**(2):173-87.
99. Glenn D, Golinelli D, Rose RD, et al. Who Gets the Most Out of Cognitive-Behavioral Therapy for Anxiety Disorders?: The Role of Treatment Dose and Patient Engagement. *Journal of consulting and clinical psychology* 2013;**81**(4):639-649.
100. Wootton BM. Remote cognitive-behavior therapy for obsessive-compulsive symptoms: A meta-analysis. *Clinical Psychology Review* 2016;**43**(Supplement C):103-113.
101. Mohr DC, Ho J, Duffecy J, et al. Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: a randomized trial. *Jama* 2012;**307**(21):2278-2285.
102. Mohr DC, Vella L, Hart S, Heckman T, Simon G. The effect of telephone-administered psychotherapy on symptoms of depression and attrition: A meta-analysis. *Clinical Psychology: Science and Practice* 2008;**15**(3):243-253.
103. Moss-Morris R, McAlpine L, Didsbury L, Spence M. A randomized controlled trial of a cognitive behavioural therapy-based self-management intervention for irritable bowel syndrome in primary care. *Psychological medicine* 2010;**40**(1):85-94.
104. Carroll KM, Rounsaville BJ. Computer-assisted therapy in psychiatry: Be brave—it's a new world. *Current psychiatry reports* 2010;**12**(5):426-432.
105. Christensen H, Griffiths KM, Farrer L. Adherence in internet interventions for anxiety and depression: systematic review. *Journal of medical Internet research* 2009;**11**(2).
106. van den Akker LE, Beckerman H, Collette EH, Eijssen ICJM, Dekker J, de Groot V. Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple

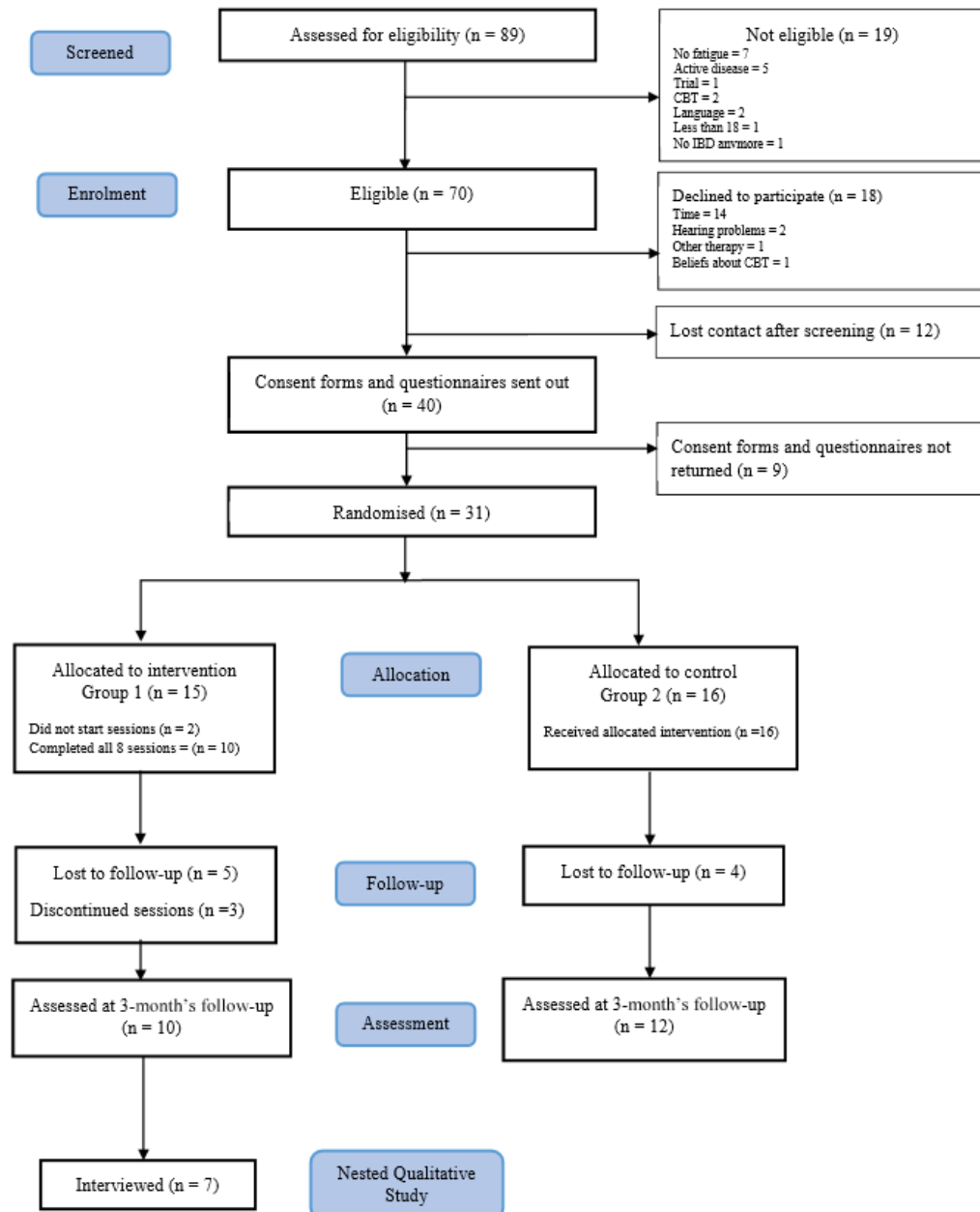
- sclerosis: A systematic review and meta-analysis. *Journal of Psychosomatic Research* 2016;**90**(Supplement C):33-42.
107. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA. What influences recruitment to randomised controlled trials? a review of trials funded by two UK funding agencies. *Trials* 2006;**7**.
108. Crutzen R, Viechtbauer W, Spigt M, Kotz D. Differential attrition in health behaviour change trials: a systematic review and meta-analysis. *Psychology & health* 2015;**30**(1):122-134.
109. Boutron I, Guittet L, Estellat C, Moher D, Hróbjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS medicine* 2007;**4**(2):e61.
110. Freedland KE, Mohr DC, Davidson KW, Schwartz JE. Usual and Unusual Care: Existing Practice Control Groups In Randomized Controlled Trials of Behavioral Interventions. *Psychosomatic medicine* 2011;**73**(4):323-335.
111. Christensen H, Hickie IB. E-mental health: a new era in delivery of mental health services. *Medical Journal of Australia* 2010;**192**(11):S2.
112. Musiat P, Tarrier N. Collateral outcomes in e-mental health: a systematic review of the evidence for added benefits of computerized cognitive behavior therapy interventions for mental health. *Psychological medicine* 2014;**44**(15):3137-3150.
113. Musiat P, Schmidt U. Self-help and stepped care in eating disorders. *The Oxford handbook of eating disorders* 2010:386-401.
114. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *Journal of evaluation in clinical practice* 2004;**10**(2):307-312.
115. Walsh A, Ghosh A, Brain A, et al. Comparing disease activity indices in ulcerative colitis. *Journal of Crohn's and Colitis* 2014;**8**(4):318-325.
116. Ratnakumaran R, Warren L, Gracie DJ, et al. Fatigue in Inflammatory Bowel Disease Reflects Mood and Symptom-reporting Behavior Rather than Biochemical Activity or Anemia. *Clinical Gastroenterology and Hepatology* 2017.
117. Dodd S, White IR, Williamson P. A framework for the design, conduct and interpretation of randomised controlled trials in the presence of treatment changes. *Trials* 2017;**18**(1):498.

Figure 1: CONSORT Flow Chart

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CONSORT

TRANSPARENT REPORTING of TRIALS



Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

Chapter 7

7 Discussion

This chapter presents a summary of the key findings of this PhD project and the key findings in relation to the research questions and the wider and relevant literature. Some of the project phases are addressed simultaneously, reflecting an iterative process of intervention development as advised by the MRC framework. Furthermore, as these questions are intrinsically linked and answered by the same study, questions relating to the feasibility of the intervention and of the trial protocol will be addressed together in *Section 7.2.4*. Subsequently, the chapter covers critiques to the study, including strengths and limitations of the theoretical framework, the theory and the methods used. Implications for the findings overall are then discussed in *Sections 7.4 Implications for research and Section 7.5 Implications for practice*. Future plans and conclusions are provided.

7.1 Summary of key findings

The systematic review study (Artom et al., 2016a; PhD Paper 1) identified eight interventions tested to address IBD-fatigue. Of these, only four were specifically designed to target fatigue: two psychosocial, one behavioural and one pharmacological intervention. There were promising, short-term effects for psychosocial and behavioural interventions, including solution-focused therapy, stress-management and exercise. Overall, a need for more interventions for the management of fatigue was established. IBD-fatigue was significantly associated with modifiable clinical and psychosocial factors including disease activity, depression, and anxiety and sleep difficulties. However, most studies were cross-sectional; thus the direction of causation remains unknown. Further exploration of the interplay between these physical and psychosocial factors utilising observational studies was suggested by the systematic review findings.

In the cross-sectional study (Artom et al. 2016b; PhD Paper 2), disease activity was the only clinical factor consistently associated with severity and impact of fatigue and QoL. Emotional, cognitive and behavioural factors were associated with fatigue and QoL above and beyond the influence of sociodemographic and clinical factors. Negative fatigue perceptions were significantly associated with severity of fatigue. Negative fatigue perceptions, all-or-nothing and avoidance behaviours were significantly associated with impact of fatigue. Additionally, disease activity together with currently taking steroids were significantly associated with worse QoL. The study findings indicated that emotional and behavioural factors and patients' negative fatigue perceptions, may be the key factors to be addressed to improve fatigue, possibly through psychological therapy.

For the pilot RCT study (Artom, 2018; PhD Paper 4), feasibility progression criteria assessing completeness of outcome measures and compliance were met, those of recruitment and retention were not fully achieved. Initial estimates of efficacy with per protocol analysis showed a reduction in fatigue scores and an improvement in QoL scores at 3-months post-randomisation. The difference in change in scores between the intervention the control group was significant for impact of fatigue on daily activities. The intervention was acceptable to participants and feasible for therapists to deliver. HCPs reported that the intervention would be broadly applicable but time, finance and training constraints may limit its implementation. Results of the pilot study indicated that a full-scale effectiveness RCT to test effectiveness and cost-effectiveness of CBT for IBD-fatigue was feasible and has a potential for improvement of fatigue with some changes to the protocol. Considering online interventions with therapist support sessions may have the potential to reduce demand on clinicians and lower costs whilst still maintaining a personalised approach to patients.

7.2 Key findings in relation to the PhD research questions and the wider literature

This study set out to develop a complex intervention for the management of fatigue and test its feasibility and potential efficacy in patients with IBD. To achieve the overall study aim, a series of questions were posed. In order to answer the study research questions, a systematic review study (PhD Paper 1), a quantitative cross-sectional study (PhD Paper 2), intervention development with a patient and public involvement activity and a pilot RCT (PhD Papers 3 & 4) were conducted guided by the *development* and the *feasibility and piloting* phases of the second version of the MRC framework (Craig et al., 2008) for complex interventions. Self-regulation theory (Leventhal et al., 1980) was utilised as the theoretical basis of the intervention.

7.2.1 Which available interventions for the management of fatigue have been identified and previously tested in patients with IBD?

The research question was answered by a systematic review of available interventions for the management of IBD-fatigue (Artom et al., 2016a; PhD Paper 1), which identified the evidence-base and fulfilled Step 1 of the *development phase* of the MRC framework. Findings from the systematic review informed decision-making on the type of intervention to be developed and whether existing research could be replicated or adapted for the development of the PhD intervention. At the time of the review, eight interventions had been tested to address IBD-fatigue. Of these, only four were specifically designed to target fatigue: two psychosocial, one behavioural and one pharmacological intervention. The two psychosocial interventions tested solution-focused therapy following pilot testing (Vogelaar et al., 2011) and at 6 months' follow-up in a full-scale RCT (Vogelaar et al., 2014) and reported significant positive effects on fatigue and

QoL. However, the effects were not maintained at 9 months. The behavioural pilot RCT (McNelly et al., 2016) compared exercise advice, omega-3 fish oil, a dietary consultation and placebo and found that participants who received advice to initiate physical activity had lower fatigue levels measured by the IBD-F scale compared to those receiving exercise placebo at end of treatment. Lastly, in an open label pilot study (Costantini and Pala, 2013) assessing the effects of thiamine on fatigue, 10/12 patients had a complete remission of fatigue. Yet, extensive methodological limitations demanded caution in the interpretation of the findings. Overall, there was judged to be a need for more interventions for the management of fatigue. The promising outcomes of psychological therapy to improve fatigue contrasted with the lack of knowledge regarding the underlying physiological mechanisms of IBD-fatigue (Kreijne et al., 2015) and the methodological weaknesses of pharmacological interventions, warranted the exploration of a psychosocial intervention for the PhD project. Yet the lack of long-term effects of existing psychosocial interventions prompted the need to conduct further development work to add to the evidence-base prior to intervention design.

More recent studies, published after the publication of the systematic review (Artom et al., 2016a) have left the landscape of interventions for the management of IBD-fatigue relatively unchanged, with a suggested potential advantage of psychosocial versus pharmacological interventions. Adding to the promising evidence for psychosocial interventions for IBD-fatigue, one non-pharmacological open label study (Szigethy et al., 2016) assessed the effects of 2-4 sessions of brief behaviour therapy for sleep over 4 weeks (Phase 1) and maintenance therapy alone or with bupropion (unicyclic, aminoketone antidepressant) added over 8 weeks (Phase 2). There was a significant decrease in fatigue measured by the Multidimensional Fatigue Inventory (MFI) following Phase 1 and a significant change over time of the MFI in the brief behaviour therapy for sleep + bupropion group after Phase 2. Conversely, pharmacological interventions for IBD-fatigue are still in a developmental state with mixed findings (Kreijne et al., 2015). One pharmacological open label study (Goodhand et al., 2016) assessed the effects of ferrous sulphate (200 mg twice daily) in 43 adolescents and 45 adults with IBD and iron deficiency anaemia. After 6 weeks of treatment with ferrous sulphate, there was no significant difference in fatigue level measured with the MFI scores. Similarly, in a randomised placebo controlled trial (Scholten et al., 2017) investigating the effect of surplus oral vitamin B12 supplementation on fatigue in patients with IBS or IBD there was no significant difference in scores of the Checklist Individual Strength subscale 'subjective fatigue' between the intervention group and the control group. Lastly, an observational study (Karlsen et al., 2017) investigated whether serum drug concentration or anti-drug antibodies of adalimumab influenced severity of fatigue. Assessing fatigue in 75 IBD patients with the Fatigue Severity Scale and in 87 IBD patients with the fatigue

Visual Analogue Scale, fatigue levels were not influenced by serum concentrations of adalimumab, nor by presence of anti-drug antibodies.

The finding that ferrous sulphate does not significantly change fatigue scores (Goodhand et al., 2016), is consistent with evidence from the PhD systematic review (Artom et al., 2016a) demonstrating no significant correlations between iron deficiency and fatigue. Indeed, this finding implies that although patients with IBD should be screened for iron-deficiency and non-iron-deficiency anaemia, other non-anaemic causes of fatigue should always be considered (Hou et al., 2016). Contrariwise, the absence of significant effects of oral vitamin B12 (Scholten et al., 2017) supplementation is somewhat conflicting with previous evidence. Indeed, it is known that vitamin B deficiency can cause fatigue (Butler et al., 2006), and evidence from both a small pilot study (Costantini and Pala, 2013) testing high-dose thiamine supplementation and an observational study (van Langenberg and Gibson, 2014) included in the PhD systematic review (Artom et al., 2016a) showed positive effects of vitamin B group supplementation on fatigue. Nonetheless, the study (Scholten et al., 2017) used <150 pmol/L as cut-off point when there is no consensus on the optimum cut-off for B12 deficiency (Battat et al., 2014). It may therefore be possible that Scholten and colleagues (2017) utilised a too lenient cut-off for B12 deficiency, thus not achieving significant changes as a result of the B12 supplementation intervention. Furthermore, prevalence of vitamin B12 deficiency has been shown to be low in IBD (Bager et al., 2011). Taken together these findings support the notion that nutrient status should be restored if necessary through dietary modification and use of supplementation (Kreijne et al., 2015), yet there is a considerable proportion of patients for whom fatigue will not respond to pharmacological treatments for biochemical conditions (*e.g.* anaemia) or to disease-modifying medication. For these patients the development of other forms of intervention targeting non-biochemical factors associated with fatigue is necessary, further justifying continued study of psychosocial factors and interventions in IBD-fatigue.

7.2.2 Which potentially modifiable physical and psychosocial factors are associated with fatigue in patients with IBD?

The research question was answered by a systematic review assessing targets for health interventions in IBD-fatigue (Artom et al., 2016a; PhD Paper 1) and a cross-sectional study assessing the contribution of clinical and psychosocial factors to fatigue (Artom et al. 2016b; PhD Paper 2). Setting-out to identify the evidence-base to fulfil Step 1 of the *development phase* of the MRC framework, the systematic review (Artom et al., 2016a) evaluated modifiable physical and psychosocial factors associated with fatigue in patients with IBD which could be targeted in the PhD intervention. Subsequently, aiming to identify components of the intervention and appropriate theory to fulfil Steps 2a & 2b of the *development phase* of the MRC framework, the

cross-sectional study (Artom et al. 2016b) addressed the need for further exploration of modifiable cognitive (*i.e.* illness perceptions, symptom focus) and behavioural factors (*i.e.* avoidance, all-or-nothing behaviours) associated with IBD-fatigue which were lacking in the systematic review (Artom et al., 2016a) and their interrelation with physical factors. Indeed, there is increasing recognition regarding the importance of cognitive and behavioural factors in the perpetuation and maintenance of fatigue symptoms in chronic conditions above and beyond the role of socio-demographic and clinical factors (Skerrett and Moss-Morris, 2006, Donovan et al., 2007). Drawing from interventions in other long-term conditions such as cancer, MS and rheumatoid arthritis (Gielissen et al., 2006, van Kessel et al., 2008, Hewlett et al., 2011), evidence shows that primary disease factors trigger the initial symptoms and how people respond to their fatigue cognitively, behaviourally and emotionally may then perpetuate or worsen fatigue. The cross-sectional study (Artom et al. 2016b) was thus undertaken to evaluate the relationship between fatigue and primary disease factors and the relationship between fatigue and cognitive, behavioural and emotional factors in order to corroborate the appropriateness of developing an intervention based on self-regulation theory principles in IBD.

Physical factors

In line with models of fatigue developed in other long-term conditions based on self-regulation theory (Skerrett and Moss-Morris, 2006), a consistent positive association was found between fatigue and IBD disease activity in both the systematic review (Artom et al., 2016a) and the cross-sectional study (Artom et al. 2016b). The relationship between IBD-fatigue and disease activity was also established by other observational studies (Tew et al., 2016, Williet et al., 2016, Huppertz-Hauss et al., 2017, Jonefjäll et al., 2017, Ratnakumaran et al., 2017) published after the systematic review (Artom et al., 2016a). Patients with higher disease activity levels measured by standard clinical indices reported higher levels of severity of fatigue and/or impact of fatigue on daily activities. Moreover, the relationship between fatigue and active disease has also been shown in other inflammatory, relapsing and remitting conditions including: rheumatoid arthritis (Singh et al., 2014), MS (Patejdl et al., 2016) and systemic lupus erythematosus (Jump et al., 2005). The established association between IBD-fatigue and disease activity, confirms the notion that primary disease factors may trigger initial symptoms of fatigue in patients with IBD. Fatigue may therefore be part of a sickness behavioural response evoked by pro-inflammatory cytokines to inflammatory and danger signals from an activated immune system (Dantzer et al., 2008). Targeting the underlying inflammatory disease as a first line strategy with pharmacological treatment may thus decrease inflammation and in turn reduce fatigue. Likewise, patients with active disease should not be included in psychosocial interventions for IBD-fatigue management as the targeting of perpetuating psychosocial factors will not be effective if the active disease triggering their fatigue is left untreated.

Nonetheless, across studies, disease activity has been assessed by different criteria, cut-offs and combinations including: i) faecal calprotectin; ii) standard clinical indices; iii) endoscopic, radiological, and/or haematological investigations (Artom et al., 2016a) and findings may vary according to measurements used. Indeed, in contrast to studies utilising standard clinical indices, others have shown no difference in fatigue scores according to faecal calprotectin (Ratnakumaran et al., 2017, Huppertz-Hauss et al., 2017) or C-reactive protein (Huppertz-Hauss et al., 2017). It is surprising for Simple Clinical Colitis Activity Index (SCCAI) (Walmsley et al., 1998) scores and not faecal calprotectin to be associated with fatigue, as the SCCAI has previously shown to correlate well with activity measures (Higgins et al., 2005). Conversely, poor correlation between the Harvey Bradshaw Index (HBAI) (Harvey and Bradshaw, 1980) and mucosal inflammation (Gracie et al., 2016, Peyrin-Biroulet et al., 2016a) may explain in part why subjectively perceived disease activity and objective inflammation markers have different relationships with fatigue in CD. It has been suggested that standard clinical index scores of disease activity may be influenced by psychological comorbidities (Gracie et al., 2016) and that in turn psychological comorbidities may also be associated with the reporting of higher levels of fatigue (Ratnakumaran et al., 2017). Caution is therefore applied in the interpretation of findings utilising standard clinical indices only. In order to unravel this problem further, future studies should therefore consider the inclusion of a faecal calprotectin measurement and/or an endoscopic evaluation to be used in addition to standard clinical indices.

Psychosocial factors

The systematic review showed a significant association between fatigue and depression, anxiety and sleep difficulties across studies. These findings have subsequently been confirmed by studies published after the PhD systematic review (Artom et al., 2016a), where a significant association between fatigue, depression, affective spectrum disorders and mental co-morbidity was present (Bager et al., 2017; Coates et al., 2017, Huppertz-Hauss et al., 2017). The positive relationship between sleep problems and fatigue was also confirmed (Hashash et al., 2017, Huppertz-Hauss et al., 2017). Additionally, addressing a gap identified by the systematic review (Artom et al., 2016a), the cross-sectional study (Artom et al. 2016b) showed a significant association between fatigue and cognitive factors such as perceptions of fatigue. Mirroring other conditions (Skerrett and Moss-Morris, 2006, Chilcot et al., 2016), more negative fatigue perceptions were significantly associated with fatigue severity. Additionally, more negative fatigue perceptions, avoidance and all-or-nothing behaviours were significantly associated with impact of fatigue on daily activities. Further substantiating the applicability of self-regulation theory for the understanding of IBD-fatigue, the established associations between IBD-fatigue and psychosocial factors adds support to the notion that how people respond to their fatigue cognitively,

behaviourally and emotionally may then perpetuate or worsen fatigue across conditions (Van Kessel and Moss-Morris, 2006). People who are depressed or anxious, may have a more negative emotional representation of their fatigue and consequently initiate negative coping procedures directed at emotion management. The adoption of maladaptive sleep patterns in response to their fatigue may lead to the exacerbation of symptoms. Furthermore, those with more negative perceptions about their fatigue may develop more maladaptive cognitions and behaviours (*i.e.* avoidance and/or all-or-nothing behaviour) in relation to their fatigue, with consequent worsening of the impact of fatigue on their lives (Hagger et al., 2017).

Added support for the relevance of fatigue-related cognitions in the IBD population comes from a qualitative study by Jordan et al. (2017). The study explored the experience of people with IBD and moderate-severe symptoms of anxiety/low mood to identify psychological processes which could be targeted in interventions. Interviews found that when participants had negative perceptions about the consequences of their IBD and their IBD-fatigue they described all-or-nothing behavioural responses, where they cycled between periods of excessive occupational activity followed by periods of retreat. This entailed working extended hours and taking on more whilst feeling well, to compensate in advance for future periods of reduced functioning due to illness. In turn this boom-or-bust behaviour was described by participants as having negative consequences in that it led to further tiredness or fatigue and underperformance at work. Adopting all-or-nothing behavioural responses may therefore be unhelpful for people with IBD in that it may precipitate or maintain fatigue which could perpetuate concerns and maintain anxiety levels.

Overall, these findings are in line with a transdiagnostic cognitive-behavioural perspective (Harvey, 2004) which proposes that similar cognitive-behavioural treatment can be used across different conditions and that fatigue may respond to similar treatment approaches regardless of the specific diagnosis or the trigger of disease-related factors. By adopting this view, which is already established in symptoms such as chronic pain (Crowe et al., 2017), core individual clinical precipitating factors underling symptoms are addressed first and common processes that perpetuate and maintain symptoms are subsequently addressed through CBT (Chalder and Willis, 2017). Quantitative (Jones et al., 2009, Kwakkenbos et al., 2015) and qualitative studies (Czuber-Dochan, 2015), and systematic reviews (Czuber-Dochan et al., 2013a, Artom et al., 2016a) have shown similarities in the perceived experience of fatigue between different disease groups. Likewise, a recent study (Ali et al., 2017) demonstrated comparability in symptom-related cognitions and behaviours across autoimmune rheumatic diseases and chronic fatigue syndrome. The overlap of cognitive, behavioural and emotional factors associated with fatigue between IBD and other long-term conditions found by the cross-sectional study (Artom et al., 2016b) thus

implies that targeting unhelpful beliefs across conditions may be a viable therapeutic objective for the management of fatigue for patients in disease remission.

7.2.3 Which mechanisms of change are relevant, acceptable and useful when developing an intervention for the management of fatigue to patients with IBD?

Building on the findings from the previous phases of the PhD study, the research question was answered by a Patient and Public Involvement activity. The Patient and Public Involvement activity aimed to use patient and HCPs perspectives to inform the adaptation of an intervention for MS-fatigue to IBD-fatigue, fulfilling step 3 of the *development phase* of the MRC framework. A cognitive-behavioural intervention for MS-fatigue (van Kessel et al., 2008) was chosen as the basis for the intervention, based on the results of the PhD systematic review (Artom et al., 2016a) and the PhD cross-sectional study (Artom et al. 2016b) which highlighted the importance of cognitive, behavioural and emotional factors in association with IBD-fatigue. The process of adaptation of the MS-fatigue intervention to the IBD-fatigue intervention is similar to the one conducted by others in adapting this MS-fatigue intervention (van Kessel et al., 2008) to cancer (Corbett et al., 2016) and renal fatigue (Picariello et al., 2018). The MS intervention had promising results in reducing levels of MS-fatigue (van Kessel et al., 2008) and incorporated in-depth mediation analysis (Knoop et al., 2012) demonstrating the significance of changing perceptions of fatigue in decreasing the severity of fatigue. Following a logic model (Figure 6, p. 58) focused on changing negative emotions and unhelpful cognitions and behaviours in relation to fatigue, the PhD intervention therefore aimed to break the vicious cycle of fatigue, ultimately reducing its severity and impact on QoL. Findings from the Patient and Public Involvement activity informed the adaptation of a CBT intervention for the management of IBD-fatigue, of which the protocol is published as Paper 3 (Artom et al., 2017) and the results are presented as Paper 4 (Artom, 2018; submitted).

Iterative work with both patients and HCPs who work with patients with IBD was then conducted in order to tailor the intervention to IBD patients. By conducting this process with Patient and Public Involvement groups, intervention manual development is not conceptualised as a single event but as a series of progressive stages in which the manual is refined to fit users' needs (Carroll and Nuro, 2002). Findings from the Patient and Public Involvement activity showed that the content of the manual was perceived as useful and relevant in helping people with IBD manage their fatigue. Specifically, in line with the therapeutic objectives of the intervention, information regarding cognitive-behavioural mechanisms of fatigue were considered particularly relevant to participants' experience of IBD-fatigue. Consistent with a transdiagnostic approach to fatigue management, it was therefore postulated that mechanisms of change based on modification of cognitive-behavioural factors related to fatigue in MS (Van Kessel and Moss-Morris, 2006) were

relevant, acceptable and useful to patients with IBD. Aside from adding more IBD-specific examples, participants suggested no changes to the therapeutic content of the manual.

7.2.4 What is the feasibility of an intervention for the management of fatigue in patients with IBD? & What is the feasibility of a trial protocol for delivering a full pragmatic RCT of an intervention for the management of fatigue in patients with IBD?

The research questions were answered by a pilot intervention study with a nested qualitative component (Artom, 2018; submitted; Paper 4) which aimed to test procedures and estimate recruitment and retention, covering the *feasibility and piloting* phase of the MRC framework. Progression criteria for continuation to a full-scale RCT relating to the feasibility of the intervention and feasibility of the trial protocol were set. Feasibility progression criteria assessing completeness of outcome measures and compliance were met, with a low proportion of missing item responses in questionnaires and 90% reported compliance rates to reading the intervention manual. Progression criteria of recruitment and retention were not fully achieved, with 44% of eligible participants consenting for participation, a withdrawal rate during treatment of 23% and a loss to follow-up rate of 29%. The intervention was acceptable to patients and feasible for the CBT therapists to deliver. However, HCPs identified potential barriers to the feasibility of implementation of the intervention in clinical practice. Overall these findings suggested a full-scale effectiveness RCT testing CBT for IBD-fatigue is feasible with some changes to the protocol.

The high level of completeness of the outcome measures suggested that the measures used were acceptable to patients (Brédart et al., 2002). Evidence shows that involving patients can be beneficial in assessing the appropriateness, wording and timing of research instruments (Brett et al., 2014). As such, the development of the questionnaire booklets together with Patient and Public Involvement may have enhanced the acceptability of the outcome measures. Likewise, the high levels of compliance for participants who started the intervention, indicated the acceptability of the intervention tasks. The choice of adapting an existing CBT intervention for MS-fatigue (van Kessel et al., 2008) which has already proven to be an acceptable treatment option for patients with MS-fatigue, may have aided in increasing participant compliance with the intervention tasks. Further confirmation of the acceptability of the intervention to patients was evidenced from interviews with participants in the CBT intervention group. Participants reported having a positive experience of taking part in the intervention, providing encouraging views on the intervention manual and the modality of communication of the therapy sessions. Similarly, at the end of the intervention delivery the therapists stated that they would use this intervention for the management of IBD-fatigue in the future, implying the feasibility of delivery of the

intervention. Indeed, the use of a treatment manual may have been beneficial in helping the therapists feel more guided and supported in delivering the treatment (Langer et al., 2011).

Clinical trials are harder to recruit for than observational studies due to the greater commitment from participants in terms of time (Newington and Metcalfe, 2014). The lower than expected consent for participation highlighted that time commitment required for the intervention may be a potential barrier to the uptake of a full-scale CBT trial for IBD-fatigue (Moss-Morris et al., 2010). Indeed, CBT takes on a collaborative stance that encourages patients to work together with the therapist on changing how they feel by applying what they have learned. Aside from reading the intervention manual and undertaking the sessions with the therapist, CBT often requires patients to spend additional time completing tasks related to the intervention. As change is assumed to take place in between therapy sessions, homework is important in enabling that change (Williams and Garland, 2002, Bannink, 2017). For a predominantly young, working population of patients with IBD-fatigue, spending time undertaking the intervention tasks on top of their daily commitments may be very difficult. Qualitative research (Czuber-Dochan et al., 2013b, Beck et al., 2013) has shown that IBD-fatigue limits patients' in their everyday lives and patients spend their energy on activities of high importance to them (*i.e.* family and work). If participants perceive that the study would not sufficiently benefit them, they may not be motivated to prioritise participation over their daily activities (Locock and Smith, 2011).

Other reasons for the slightly lower than expected recruitment rates may be related to the characteristics of the study population. In a study exploring the characteristics of non-responders to self-reported questionnaires in an IBD-cohort study (Multone et al., 2015), age > 50, female gender and longer disease duration were identified as factors inversely associated with non-response. Reported signs and symptoms of depression were also a risk factor for non-response. The latter finding is in line with evidence showing that patients with mood disorders (Mein et al., 2012) are at higher risk of non-response in studies. Unfortunately, due to ethical reasons, socio-demographic and clinical data for those who did not consent to participate could not be recorded in the PhD intervention study. Nonetheless, the baseline characteristics of those who consented (*i.e.* 65% female gender, mean age of 38, median time since diagnosis of 16 years), suggest different socio-demographic subgroups of the population may have been more willing to participate. Furthermore, with a high comorbidity between IBD-fatigue and depression (Artom et al., 2016a) and high levels of depression reported in this intervention study (mean PHQ = 10.87), it is possible that their depressive symptoms may make patients with IBD-fatigue a particularly difficult group to recruit. Strategies to improve recruitment in future trials could include: having a dedicated research nurse for recruitment at each site, recruiting through charity networks such

as CCUK and engaging participants at the start of the programme by better highlighting the benefits of the research in its early stages (Donkin and Glozier, 2012).

Despite not achieving the pre-defined progression criteria, findings relative to retention of participants are comparable to or higher than other pilot psychosocial studies in IBD across different modalities of intervention delivery (Vogelaar et al., 2011, Mikocka-Walus et al., 2015, Schoultz et al., 2015). A study testing individual, face-to-face, psychological interventions (*i.e.* solution-focused and problem-solving therapy) for IBD-fatigue (Vogelaar et al., 2011), reported a during treatment withdrawal rate of 21%. Investigating the efficacy of online CBT for managing anxiety and depression in IBD, Mikocka-Walus et al. (2015), reported a 33% loss to follow-up rate at 6 months and a 56% loss to follow-up at 24 months. In a trial comparing group mindfulness-based cognitive therapy vs. wait-list control for depressive symptoms and stress in IBD (Schoultz et al., 2015), the during treatment withdrawal rate was 45% and the loss to follow-up rate was 41%. It is hence possible that the progression criteria for retention in the PhD intervention were set unrealistically high.

Alternatively, one participant who dropped out at session 4 reported feeling that the intervention was not suitable to him as his fatigue was not severe enough. Therefore, low retention rates may have been due to the threshold for fatigue at enrollment being set too low. Additionally, other reasons could also explain low retention rates. Participants may have had unrealistic perceptions around the benefits of the intervention (McDonald et al., 2006). Similarly, participants may not have fully comprehended the impact of psychotherapy at the start of the intervention and thus have been reluctant to further participate after the first sessions (Vogelaar et al., 2011). Furthermore, if participants perceived contact with staff to be insufficient during the study, they may not feel supported enough to remain engaged in the trial (Mikocka-Walus et al., 2017). Lastly, participants may not have persisted with the intervention because they believed that the research was not important enough or were not invested in participating in the research from the start. Indeed, evidence shows that people who participate in research trials are more likely to view research more favourably (Madsen et al., 2002). Strategies to improve retention may include: outlining the exact time requirements of participation in the invitation materials so that participants are more aware of what to expect, offering more flexible appointment times (Attwood et al., 2016) and the use of web-based data collection which reduces time associated with study participation (Akmatov et al., 2017).

HCPs found a broad applicability and usefulness of the intervention to their IBD patient group. Indeed, consistent with previous qualitative (Czuber-Dochan et al., 2014b) and quantitative research (Dibley et al., 2017), HCPs reported struggling to help patients with IBD-fatigue. The

intervention was thus seen as a promising addition to the limited array of interventions recommended by HCPs to manage IBD-fatigue. However, no current member of the IBD team was seen to have enough time and adequate training to deliver the intervention in its current format. Doctors were unlikely to have capacity to deliver the intervention and availability of financial resources to employ an external therapist to deliver the CBT intervention was also perceived as limited. The identified lack of resources is consistent with the knowledge that the UK NHS is currently under-funded and overstretched. Eighty-five percent of physicians believe that the current health funding is insufficient to meet the rising demand for health services, the number of medical and nursing students has fallen and NHS staff increasingly feel like collateral damage in the battle between rising demand and squeezing budgets. Even the most useful and effective intervention will be worthless if it cannot be implemented into clinical practice, and inadequate training of practitioners and lack of funding are among the two principal factors which contribute to the limited translation of evidence-based approaches (Glasgow and Emmons, 2007). As such, despite the positive views of HCPs regarding the use of the intervention, identified barriers to implementation need to be addressed prior to the progression of the study to a full-scale RCT. This should be done by integrating an economic evaluation in the full-scale RCT to demonstrate cost-effectiveness (Glasgow and Emmons, 2007) and finding less resource intensive modalities of delivery of the intervention such as online interventions (Griffiths et al., 2010).

Barriers to implementation of the intervention were similarly identified in the original MS-fatigue trial (van Kessel et al., 2008). Despite promising results of the face-to-face CBT for MS-fatigue, few MS services have access to a CBT therapist. Consequently, a mixed method pilot RCT of an internet-based version (Moss-Morris et al., 2012) of the therapist-delivered CBT intervention for MS-fatigue (van Kessel et al., 2008) was trialed. The online intervention consisted of eight, interactive, tailored weekly sessions. Participants received three telephone support sessions of between 30–60 min, while they worked through the programme. Large between group treatment effects were found for the primary outcomes of fatigue severity ($d = 1.19$) and impact ($d = 1.02$). The online CBT group also reported significantly greater improvements in anxiety, depression and quality-adjusted life years. Internet delivery of the intervention was acceptable to most participants and cost-effective. Additionally, this internet-based version was subsequently piloted in New Zealand (van Kessel et al., 2016) to compare use of the website only (MSInvigor8-Only) with use of the website plus email-based therapy support (MSInvigor8-Plus). The MSInvigor8-Plus condition resulted in significantly greater reductions in fatigue severity and impact compared with the MSInvigor8-Only condition. Large between-group effect sizes for fatigue severity ($d = 0.99$) and fatigue impact ($d = 0.81$) were found. These findings therefore suggest that online CBT interventions for the management of fatigue may be feasible, potentially effective and cost-

effective. Yet providing regular support alongside the website may have added benefits in terms of adherence to the programme and improvements of fatigue outcomes.

7.2.5 What are the initial estimates of efficacy of an intervention for the management of fatigue in patients with IBD?

The research question was answered by a pilot intervention study with a nested qualitative component (Artom et al., 2017; PhD Papers 3&4). There were greater improvements at 3-months post-randomisation in severity and impact of fatigue and QoL for the intervention group compared to the control group, yet these differences were significant only for impact of fatigue. Preliminary efficacy analysis from the study thus indicates that changing IBD-patients' feelings, cognitions and behaviours in relation to fatigue may improve the impact that fatigue has on their lives. Consistent with results of CBT interventions in other conditions such as MS (van Kessel et al., 2008), rheumatoid arthritis (Hewlett et al., 2011) and cancer (Gielissen et al., 2006, Goedendorp et al., 2010), results of the intervention suggest that CBT is effective in targeting perpetuating factors of fatigue in IBD-patients in remission. Once modifiable primary disease and clinical factors shown to trigger IBD-fatigue in the systematic review (Artom et al., 2016a) have been managed through pharmacological interventions, modifiable psychosocial factors shown to perpetuate IBD-fatigue in the cross-sectional study (Artom et al. 2016b) can be managed through non-pharmacological interventions based on cognitive-behavioural models.

Utilising sections I and II of the IBD-Fatigue scale (Czuber-Dochan et al., 2014a), the intervention study (Artom et al., 2017) aimed to determine the effects of CBT on both the severity of, and impact of, fatigue. Impact is not the same as fatigue severity and the inclusion of measures of perceived severity and impact of fatigue on daily life is advised to better elucidate intervention effects on fatigue (Joseph et al., 2015). Indeed, fatigue severity does not reflect a person's perception and appraisal of the fatigue and measuring only fatigue severity can fail to capture differences in the experience of fatigue. If a decrease is seen in fatigue severity and the impact of fatigue remains high, it can imply that a patient still suffers and is disabled due to fatigue. The patient is thus not fully recovered (Knoop et al., 2007). Differences in improvements at 3-months post-randomisation for the intervention compared to the control group were significant for impact of fatigue but not severity of fatigue. The extent to which patients perceive fatigue to impact on their daily activities is individual and may be seen in the context of personal attributions (Sirois, 2009). Consequently, the significant effect of CBT on impact of IBD-fatigue on daily activities is in line with the notion that CBT can change subjective psychological factors which determine how patients experience symptoms.

Multiple explanations can be advanced for the lack of significant effects on severity of fatigue. This may be a result of the complex, multidimensional and multifactorial aetiology of fatigue in IBD (Dittner et al., 2004). Indeed, although psychological factors have been shown to perpetuate IBD-fatigue (Graff et al., 2013), inflammatory disease-related processes may still play a role in causing fatigue even when IBD is quiescent (Czuber-Dochan et al., 2013a). As such, if these inflammatory disease-related processes are not fully controlled, CBT may help to improve the impact of fatigue on patients' daily activities yet not necessarily have an effect on its severity to the same degree. Another explanation is that the sample was too small to detect meaningful differences. Alternatively, as tiredness is common in the general population, it may be difficult for patients to discriminate where experiencing fatigue as a sign of illness ends and the experience of normal daily activities (Gielissen et al., 2007). Lastly, as suggested for a CBT intervention for MS-fatigue (Thomas et al., 2014) where improvements were only shown 4 months after the intervention ended, it may be that changes may take longer to have an impact because behavioural changes are only slowly adopted in daily life. Therefore, it is possible that the effects on fatigue severity may require longer time to be evidenced compared to those on fatigue impact.

Building on the quantitative data indicating efficacy for CBT on impact of fatigue, qualitative interview data from the intervention (Artom et al., 2017) showed that participants experienced a change in the negative way they thought and felt about their fatigue. Participants highlighted that having more positive thoughts about fatigue had helped them feel better about it, ensure it had a lesser impact on their lives and ultimately manage it more effectively. Furthermore, participants identified negative behavioural strategies through the homework tasks and then modified them as a result of the CBT. In line with recent qualitative evidence in IBD (Jordan et al., 2017), all participants talked about the negative all-or-nothing behavioural patterns they had been adopting before the trial, and how the intervention had taught them to better pace their activity levels through self-monitoring, introducing breaks, planning their time effectively and learning to say no. This is consistent with self-regulation theory (Leventhal et al., 1980) which states that the way people think about their illness can have a significant impact on the way they feel about, behave in relation to and cope with their symptoms. In absence of mediation analysis this causal mechanism between changes in cognitions and changes in fatigue cannot be confirmed at this stage (Windgassen et al., 2016). However, drawing from mediation analysis conducted in the original MS-fatigue trial (Knoop et al., 2012), it may be implied that the intervention helped to break the vicious cycle of cognitive, behavioural and emotional responses to symptoms which interact with clinical factors to maintain IBD-fatigue. Future studies should therefore include mediation analysis to determine these causal mechanisms.

The non-significant effect of the intervention on IBD-specific QoL is somewhat surprising. Nonetheless, QoL scores improved in both the CBT intervention and control group, with the intervention group showing a greater increase from baseline to follow-up compared to the control group. This is consistent with other pilot studies assessing the effects of psychosocial interventions for IBD-fatigue (Vogelaar et al., 2011), depression and anxiety (Schoultz et al., 2015) and distress (Mikocka-Walus et al., 2015) where change in QoL scores did not mimic change in other outcome measures for all patients as expected. One of the possible explanations is that sample sizes in these studies was too small to detect any significance (McCombie et al., 2013). Another, is that psychotherapy may only improve QoL of life for a subgroup of patients more ‘in need’ (*i.e.* with high scores on mental health subscales), thus implying that psychotherapeutic interventions should be targeted at this group rather than the general IBD population (Mikocka-Walus et al., 2015). Lastly, it may be suggested that the CBT intervention was not as effective in improving QoL as it was at improving impact of fatigue because the intervention was designed specifically to improve fatigue, and improvements in QoL are a likely consequence of symptom improvement. Indeed, similar results have been found in a meta-analysis of CBT for eating disorders (Linardon and Brennan, 2017), where improvements in QoL were smaller compared to changes in improvements in eating disorders.

7.3 Critiques of the study

Strengths and limitations of the individual studies are described in the discussion section of each of the four published papers. Findings from the studies should be interpreted in light of these. Reflecting on this PhD project overall, critiques to the theoretical framework, the theory and the methods applied to each phase of the MRC framework to answer the research questions are discussed below.

7.3.1 Critiques of the theoretical framework

A number of strengths of the use of the MRC framework (Craig et al., 2008) to guide the development of the PhD intervention were identified. The use of the *development phase* of the MRC framework was firstly helpful in identifying the components and mechanisms that would underpin the PhD intervention in advance of piloting its efficacy. Indeed, the identification of the intervention components and mechanisms of change was key in then selecting an MS-fatigue intervention (van Kessel et al., 2008) to adapt for the management of IBD-fatigue (Haji et al., 2014). The use of the MRC framework supported the grounding of the intervention development process in a theoretical framework. Furthermore, by including a *feasibility and piloting phase*, the risk of evaluating an unfeasible intervention in a large-scale effectiveness RCT was reduced. The MRC’s guidance to incorporate qualitative methods within RCTs ensured that the PhD intervention was more appropriate and relevant to the needs of the target population. The MRC

framework's guidelines to publish piloting work, allowed for useful data from the intervention pilot to be disseminated for wider use (Reelick, 2011). The recommendation of the MRC framework to explain the decision-making process in each phase, aided in adopting a more reflective and critical approach to intervention development (Craig and Petticrew, 2013).

Limitations of the MRC framework for this PhD project were mainly related to its application. Although numerous papers reporting the utilisation of the MRC framework as guidance for the development of complex interventions were identified, examples in which the step-by-step application of the framework was described were rare (Hurley et al., 2016). Accounts of how different research methods can be utilised in intervention development were found (*i.e.* systematic reviews to identify and evaluate the evidence-base, quantitative studies to help to draw conclusions about likely intervention effects and potential effect modifiers, qualitative studies to provide an in depth understanding of relevant issues) (O'Brien et al., 2016). Nonetheless, there was a lack of clarity over the methods to be applied to each MRC phase, making it difficult to make fully informed decisions on the methods to use during the development of the PhD intervention.

A posteriori, in order to gain a better understanding of which methods have been applied by other researchers, studies which used the MRC framework were reviewed (Appendix XVIII). As a comprehensive and recent review of the evidence had already been conducted, the studies were drawn from two reviews (Corry et al., 2013, Levati et al., 2016). The systematic review by Corry and colleagues (2013) aimed to review published guidelines for intervention development and to examine how researchers have used guidelines when developing interventions. Of the 14 papers included in the review which reported the development of interventions, the 9 papers which referred to the MRC framework were included. The scoping review by Levati and colleagues (2016) aimed to identify and synthesise the available evidence relating to the strategies and methods used to optimise interventions at the pre-trial stage. Of the 27 papers included in the review, the 17 papers which referred to the MRC framework were included. Seven of the papers overlapped between the two reviews, with a total of 20 papers remaining. For each study the version of the MRC framework (Campbell et al., 2000, Craig et al., 2008) utilised and the methods applied for each phase were specified.

Overall, the brief review showed a wide variation in the ways in which studies applied the MRC framework. To identify the evidence-base most studies conducted single or multiple, systematic or non-systematic reviews. The methods utilised for the other steps of development were very different according to each study. For instance, to identify/develop theory methods included: additional literature searches, qualitative interviews, focus groups, questionnaire surveys, analysis

of registry data, content analysis of available interventions and non-participatory observation. Likewise, to model processes and outcomes qualitative interviews, focus groups, economic modelling, Delphi studies and consensus processes and non-participatory observation were used. As such, it can be hypothesised that to date investigators have no conclusive path to follow for choosing the methods to apply to each phase of the MRC framework. A further refinement of the second version of the MRC framework (Craig et al., 2008) or the integration of other frameworks such as the Steps for Quality Intervention Development proposed by Wight et al. (2015) may be helpful in filling this important methodological gap.

7.3.2 *Critiques of the theory*

The use of self-regulation theory (Leventhal et al., 1980) as the basis of the intervention was chosen as a result of the PhD systematic review (Artom et al., 2016a; PhD Paper 1) and subsequently tested by the PhD cross-sectional study (Artom et al. 2016b; PhD Paper 2). Self-regulation theory is a patient-centred and dynamic theory, in which individuals' perceptions of their illness and symptoms are constantly evolving (McAndrew et al., 2017). Its use was therefore helpful in developing an intervention which recognised patients' capacity for change through self-management. In the *development phase*, self-regulation theory was beneficial in selecting which psychosocial variables should be manipulated by the PhD intervention in order to produce the desired change in fatigue (Eccles et al., 2005). The theory was also a steppingstone in the choice of a cognitive-behavioural therapeutic modality for the intervention. The compatibility between self-regulation theory and cognitive behavioural techniques and theory has previously been demonstrated (McAndrew et al., 2008). As self-regulation theory incorporates cognitive and behavioural concepts, it is intuitive for cognitive and behavioural skills from CBT to be used to modify behaviour and challenge maladaptive cognitions which maintain poor self-regulation. In line with these tenets, it was thus postulated that CBT could be effective in modifying illness perceptions and coping responses, which in turn influence outcomes (*i.e.* lower to higher levels of fatigue). Finally, in the *modelling phase*, the use of self-regulation theory aided in enhancing the process of intervention development by drawing on effective interventions in other conditions based on cognitive-behavioural principles (Gielissen et al., 2006, van Kessel et al., 2008, Hewlett et al., 2011) without 'reinventing the wheel' (Lippke and Ziegelmann, 2008).

Grounding this PhD project in self-regulation theory was valuable to understand how people self-manage and cope with symptoms, however it is not a stand-alone approach for addressing symptoms in complex interventions (McAndrew et al., 2017). RCTs which have used self-regulation theory alone in an attempt to influence the process of self-regulative illness management are sparse (Hagger et al., 2017) and self-regulation theory is generally used as an adjunct with other therapeutic modalities (Corbett et al., 2015). Although the PhD intervention

incorporated some principles of self-regulation theory, the theory was not overtly addressed within the treatment manual or the sessions. Indeed, participants filled out the Brief Illness Perceptions Questionnaire (Broadbent et al., 2006) as part of the outcome measure booklet, yet their perceptions of fatigue were not elicited directly by the therapist. By adapting an existing manual for the management of MS-fatigue (van Kessel et al., 2008) the therapeutic content of the intervention could not be significantly altered. Mimicking research conducted in cancer fatigue (Corbett et al., 2015, 2016), in the future however, the theory could be incorporated more explicitly in both the development phase and the CBT therapeutic process in order to help the therapists develop a treatment plan more tailored to their patients' needs. By eliciting the patients' perceptions about their fatigue for instance, the therapist could then identify the perceptions which are key to improving self-management, and subsequently work with them to negotiate a shared set of more helpful fatigue perceptions (McAndrew et al., 2017).

7.3.3 Critiques of the methods

The systematic review (Artom et al., 2016a; PhD Paper 1) identified modifiable factors which had already been or could be targeted by health interventions to reduce IBD-fatigue. A systematic review study was considered appropriate to explore available interventions and potentially modifiable factors associated with IBD-fatigue, as it enabled collection of all available empirical evidence on these aspects (Higgins and Green, 2011). Indeed, the systematic review (Artom et al., 2016a) was useful in systematically evaluating the effects of existing interventions for IBD-fatigue. Nonetheless, results of a systematic review are dependent on the quality of the studies used as the primary data source (Smith et al., 2016). Although 79% of the included studies in the systematic review (Artom et al., 2016a) were high or medium quality, no studies were excluded on the basis of quality. Consequently, findings should be carefully appraised before reaching definitive conclusions. Furthermore, due to the limited number of interventions available, no clear pattern of results favouring one particular intervention type emerged. Likewise, although effects were found for psychosocial interventions, it was unclear which behaviour change techniques in the psychosocial interventions were responsible for the observed changes in fatigue. In order to overcome these barriers, in the future the application of a taxonomy of behaviour change techniques (Abraham and Michie, 2008) could help to identify what made an intervention more effective than another. Evaluating the effectiveness of the individual behaviour change components of the interventions rather than the interventions as a whole, would enhance the value of the systematic review by enabling a more informed selection of intervention components during intervention development process (Michie et al., 2009).

The cross-sectional study (Artom et al. 2016b; PhD Paper 2) evaluated the potential relationship between modifiable cognitive-behavioural factors and IBD-fatigue. A cross-sectional study was

considered appropriate to explore potentially modifiable factors associated with IBD-fatigue, as it allowed for multiple clinical and psychosocial outcomes potentially associated with IBD-fatigue to be studied at the same time (Mann 2003). Furthermore, the study enabled the assessment of fatigue in a relatively large and diverse sample of IBD patients, and across multiple hospital sites. However, causation could not be determined from data collected only at one point in time and cross-sectional studies do not provide an explanation for their findings (Price and Murnan, 2004). Since data on exposure and outcome were obtained at the same time, the direction of the association could not be established with certainty (DiPietro, 2010). Conversely, a longitudinal design would have allowed for more robust temporal associations between clinical and psychosocial factors to be assessed, together with an analysis of mediating factors. In order to overcome limitations of cross-sectional study design, 12 and 24-months' follow-up points were included in the design of the quantitative study and in the ethical approval application. Due to the limited time-frame of this PhD project, only the baseline results of the longitudinal study were analysed and included in this thesis. At the time of writing-up of the present chapter, 24-months' follow-up data are being collected. Analyses and dissemination of the longitudinal study research will follow. As fatigue has been demonstrated to be very variable, with fluctuations over time (Schwartz et al. 2000), upcoming follow-up assessment time-points will provide a more complete picture of patterns of fatigue in patients with IBD.

A Patient and Public Involvement activity informed the adaptation of a CBT intervention for MS-fatigue to IBD-fatigue. Involving end-users in the development process was useful in making the intervention more responsive to IBD-patients' needs. However, the Patient and Public Involvement activity was limited in its scope. Indeed, participants annotated comments on the intervention manual and completed a structured feedback form at only one point in time. The inclusion of more iterative phases, moving between participants' feedback and changes to the intervention, may have been helpful in providing detailed information on specific aspects of the intervention. Furthermore, in depth qualitative techniques for including Patient and Public Involvement could have been used to improve the intervention development process. Think-aloud interviews for instance, ask people to give their immediate reactions to every element of the intervention and allow researchers to also observe how it is used (Van den Haak et al., 2007). They can be important in identifying problems experienced by people when carrying out the intervention and allow modification of the intervention accordingly. Alternatively, retrospective semi-structured interviews can be valuable to evaluate people's experiences after completion of either a part of or the whole intervention. Semi-structured interviews can be complementary to think-aloud interviews because they provide information about how people use interventions in absence of the researcher, who might otherwise influence their experiences (Bradbury et al.,

2014). Additionally, diaries can enable people to keep a longitudinal record of aspects of the intervention they found helpful or unhelpful, easy or hard to use and relevant or irrelevant.

In the future, the evaluation of the PhD intervention in a full-scale RCT as an online platform could permit more comprehensive Patient and Public Involvement work with patients to be conducted with a lower expenditure of resources. In online intervention development, users are involved iteratively throughout the entire process. Initially users can help to identify the intervention objectives and key features of the intervention needed to achieve each objective. Once a prototype is created, users can test it to gain insight on whether the intervention is acceptable, interesting easy to use and feasible for people to adhere to. As user feedback is collected, changes can be made to the intervention and further Patient and Public Involvement can be conducted to determine whether the implemented changes are suitable. Lastly, after the prototype is refined users can be encouraged to use the intervention on their own in order to try behavioural changes supported by the intervention. Indeed, online interventions are typically used independently by users, and so they must be designed with an understanding of how people do this (Yardley et al., 2015). Furthermore, the application of a prioritisation method such as the MoSCoW analysis (Bradbury et al., 2014), could streamline the process of incorporating user feedback to the online intervention development. The method ranks content changes into: ‘Must’ – essential change, ‘Should’ – important but not critical content change, ‘Could’ – desirable content change and ‘Would’ – change that could improve user experience but by no means essential.

The pilot RCT (Artom, 2018; submitted; PhD Paper 4) assessed the feasibility and initial estimates of efficacy of a CBT manual with 8, weekly therapist telephone sessions vs. a fatigue information sheet without therapist help. The undertaking of a pilot study prior to a full-scale effectiveness RCT was useful in evaluating the feasibility, acceptability and efficacy of the intervention prior to rolling it out across a wide range of settings. Changes to the protocol can now be conducted in order to make the intervention trialled in the full-scale evaluation more implementable in the NHS (Craig and Petticrew, 2013). Moreover, the inclusion of a nested-qualitative study within the RCT allowed for the patient, therapist and healthcare professionals’ perspectives to be embedded in the future intervention. These perspectives led to the understanding of which components of the intervention worked to improve fatigue and potentially the reasons why. However, the small external pilot design of the study prevented the possibility of conducting mediation analysis to confirm the causal mechanisms between changes in cognitions and changes in fatigue. As such, mediation analysis should be included in the full-scale RCT for the advancement of psychological theory and refinement of clinical practice. By pinpointing mediating psychological mechanisms, therapeutic processes may be refined to focus

on specific aspects of therapy that lead to improvements in outcomes, with the possibility of discarding aspects that are less relevant. Uncovering mechanistic processes can also lead to more effective delivery of therapy and can be useful for development and enhancement of treatments that can be used transdiagnostically across different conditions, tackling a range of outcomes simultaneously (Windgassen et al., 2016).

Additionally, ethical approval permissions were not sought for the inclusion of fidelity assessments in the pilot RCT. Intervention fidelity refers to the extent to which the core components of the intervention are delivered as intended by the protocol (Bond et al., 2000). Intervention fidelity can impact both the internal validity and the external validity of these studies and has implications for the ability to attribute symptom changes to the intervention and to replicate and disseminate treatments (Perepletchikova et al., 2007). Consequently, audio-recording and fidelity coding of a subset of the sessions should be included in the full-scale RCT in order to give providers corrective feedback when the intervention is ongoing and identify potential fidelity-outcome associations at the end of the intervention (Miller and Rollnick, 2014).

7.4 Implications for research

The results of this PhD project have a number of implications for research:

- Psychosocial factors (emotional, cognitive and behavioural) are consistently associated with IBD-fatigue. Further longitudinal research can help to unravel the relationship between psychosocial and clinical factors in IBD-fatigue.
- Cognitive-behavioural factors maintaining and/or perpetuating fatigue are similar across conditions. Drawing from other conditions to develop interventions utilising a transdiagnostic approach can be helpful to develop effective interventions without re-inventing the wheel.
- Cognitive-behavioural interventions can contain complex language. The average reading age for a standard CBT intervention is 17 years (Flesch–Kincaid grade 12) (Williams and Garland, 2002). Existing interventions need to be evaluated together with patients in order to make the language appropriate to their needs.
- Patient and Public Involvement is useful in making the intervention relevant to patients' needs. More time should be planned for intervention development in order for patients to be involved iteratively throughout the intervention development process.
- In depth qualitative research is important when developing complex interventions to ensure that interventions are usable and engaging (Yardley et al., 2015). Qualitative work should be included in the intervention development phase.

- CBT is a feasible and effective therapeutic modality for the management of IBD-fatigue. Therefore test CBT in a full-scale RCT with some adaptations to the protocol.
- Low satisfaction rates were experienced in control group receiving Fatigue Information Sheet. The use of a comparison instead of a control group, *e.g.* in which intervention time is kept constant across the two groups may help to minimise the effect of patients' expectancy on attrition. The use of validity checks to test the validity of the control condition may also be beneficial. Alternatively, a different trial design such as a stepped wedge RCT which involves sequential roll-out of an intervention to participants over a number of time periods, would allow all participants to receive the CBT intervention. Indeed, this design is particularly relevant where it is predicted that the intervention will do more good than harm (Brown and Lilford, 2006).
- The telephone is an acceptable modality of delivery of support sessions. Use telephone rather than face-to-face support sessions in a full-scale RCT (Freedland et al., 2011).
- Manualised CBT with therapist support sessions may not be feasible to implement in NHS IBD services. Ways to increase the feasibility of implementation need to be identified. These could include testing the CBT manual without therapist support or the translation of the paper CBT manual to an online intervention platform.
- Interventions will only be implemented in the NHS if they are cost-effective. In depth economic analysis to calculate costs and assess potential cost-effectiveness should be included in the full-scale RCT.

7.5 Implications for practice

The results of this PhD project also have implications for practice:

- Fatigue is a prevalent and burdensome symptom for patients with IBD. Fatigue should thus be recognised and discussed and addressed in clinical practice. Likewise, care pathways for the management of fatigue should be put in place.
- High levels of psychological distress in IBD patients were identified throughout this PhD project. Having a dedicated psychologist within IBD services may be beneficial in addressing psychological issues experienced by patients with IBD and improve their QoL. This is in line with findings on HCPs views on how to best reshape existing IBD care worldwide (Mikocka-Walus et al., 2014), which suggest that an ideal IBD service should be fully integrated involving significant roles of IBD nurses, psychologists and dieticians.

7.6 Future plans

Additional publications stemming from this PhD project will be completed following submission of this thesis incorporating publications. These include: analysis of the 12 and 24-months' longitudinal data evaluating physical and psychosocial predictors of IBD-fatigue, and the 6 and 12-months post-randomisation data analysis of the pilot CBT intervention for IBD-fatigue. A secondary qualitative analysis of the qualitative interviews with patients conducted as part of the pilot RCT is also being conducted. Furthermore, being part of a larger research team at King's College London conducting work related to fatigue and IBD-symptom management has allowed me to be involved in projects related to IBD-fatigue which are not part of my PhD. Participation in these projects demonstrates my interest in IBD-fatigue and my desire to pursue further work on this topic in the future. In 2014-15 I took part in an international collaboration for a Cochrane review on interventions for fatigue in IBD. The protocol has been published (Farrell et al., 2015b), the full review will be finalised in 2018. In 2017 I co-applied with my supervisor (WCD), and obtained a European grant to translate and cross-culturally validate the IBD-Fatigue scale in seven languages. The project is now in its final phase. Funding for a 5-year National Institute for Health Research programme grant to improve the well-being of patients with IBD by reducing the burden of fatigue, pain and incontinence has been obtained by the research team in April 2016. The programme has commenced in January 2018 and in line with Internet-based work conducted in MS (Moss-Morris et al., 2012), it will include a full-scale evaluation of an online self-management intervention, health economics and process evaluation. The outcomes of the qualitative interviews included in the PhD intervention will be used to inform the development of the full-scale RCT. Having successfully obtained the position of Research Associate on the programme, my role will be to help on the development of the online intervention.

7.7 Reflection

Reflection refers to the process of thinking retrospectively on an event in order to learn from it (Mezirow, 1998); reflexivity is an active process of dynamic self-awareness which takes place as an event is happening (Downing, 2006). In qualitative research, reflexivity has emerged as a way to manage how personal understanding, knowledge and perspectives of the researcher can influence the research itself (Finlay and Gough, 2008). Although, this is not predominantly a qualitative PhD the opportunity to reflect retrospectively on the process of conducting the PhD research can be valuable in interpreting its conclusions. The principles of reflection were incorporated throughout this PhD and in the process of writing this chapter.

I believe that making the decision to write a thesis incorporating publications has influenced my experience of undertaking this PhD project. Having the opportunity to disseminate my work throughout the PhD, enabled me to receive external feedback on my research by experts in the

field from its earliest stages. Benefitting from feedback from reviewers, alongside guidance from by supervisory team, aided me to benchmark the quality of my work against what is expected within my discipline, and to better understand the nature of academic research. Publishing my research for a broader audience, fostered my sense of achievement during the course of my project and improved my motivation in progressing from one stage to the next. Additionally, having published in gastroenterology-specific journals allowed me to become an expert reviewer and attend medical conferences on IBD. Both of these experiences have been valuable in learning more about research and clinical practice in IBD. Publications are increasingly used in universities to measure performance and as a criterion for achieving academic promotion and competitive research funding. As such, it is possible that the publication of my research papers may have helped me in obtaining employment as a Post-doctoral Research Associate.

Prior to commencing my PhD, I undertook an undergraduate degree and an MSc in Psychology. With no previous medical or nursing background, I was conscious of my need to acquire knowledge on IBD from the early stages of my PhD. IBD is a complex physical illness and an understanding of its symptoms and medical management is crucial in being able to appreciate the impact of IBD on patients' QoL. Throughout my PhD I therefore took part in weekly GI multidisciplinary team meetings at one of the hospitals where I recruited for my cross-sectional and intervention studies. Taking part in these meetings allowed me to develop an awareness of the condition as a whole and better appreciate how fatigue is managed in clinical practice. Furthermore, it is possible that having formed a positive relationship with the clinical team may have helped me in engaging HCPs in my study, thus achieving better recruitment outcomes. Additionally, being embedded within the IBD clinical team, I was able to give a voice in the psychological aspects of IBD, ultimately helping to make the availability of psychological management a priority for the hospital directorate. Contributing to service development, I aided in setting-up a psychological screening programme and submitting a business case for an integrated psychological service for IBD patients.

7.8 Conclusions

This PhD provides an original contribution to the body of knowledge on feasible and effective treatments for the management of IBD-fatigue. Studies in this PhD addressed the primary need for the development of a theoretically-driven intervention to improve fatigue in patients with IBD. A number of physical and psychosocial factors which could potentially be modified through targeted health interventions and improve fatigue in IBD were identified, emphasising the importance of conducting research on factors potentially amenable to modification. Cognitive and behavioural factors, known to perpetuate fatigue in other conditions, were found to be associated with IBD-fatigue, indicating a potential for the development of transdiagnostic cognitive-

behavioural fatigue management interventions. Drawing from a theory-based, effective CBT intervention for MS-fatigue and incorporating Patient and Public Involvement activities, this PhD integrated current best evidence across conditions, patient experience and clinical expertise. The resulting intervention was the first to test the applicability of CBT treatment models for fatigue with proven effectiveness in other long-term conditions to patients with IBD. Findings for the pilot intervention indicate feasibility and potential for efficacy of CBT for the management of IBD-fatigue. A large-scale RCT is needed to investigate the size and longevity of treatment gains and the cost-effectiveness of the therapy. Incorporating changes to the protocol and developing an online intervention may be an effective way to overcome the barriers to implementation identified by HCPs and test the generalisability of the intervention to IBD-clinical practice.

8 References

- Abautret-Daly, Á., Dempsey, E., Riestra, S., De Francisco-García, R., Parra-Blanco, A., Rodrigo, L., Medina, C., Connor, T. J. & Harkin, A. 2017. Association between Psychological Measures with Inflammatory Anddisease-Related Markers of Inflammatory Bowel Disease. *International Journal of Psychiatry in Clinical Practice*, 21(3), 221-230.
- Abraham, C. & Michie, S. 2008. A Taxonomy of Behavior Change Techniques Used in Interventions. *Health Psychology*, 27(3), 379-87.
- Ahern, K. & Le Brocque, R. 2005. Methodological Issues in the Effects of Attrition: Simple Solutions for Social Scientists. *Field Methods*, 17(1), 53-69.
- Ahmad, N., Boutron, I., Dechartres, A., Durieux, P. & Ravaud, P. 2010. Applicability and Generalisability of the Results of Systematic Reviews to Public Health Practice and Policy: A Systematic Review. *Trials*, 11(1), 20-29.
- Akmatov, M. K., Jentsch, L., Riese, P., May, M., Ahmed, M. W., Werner, D., Rösel, A., Prokein, J., Bernemann, I., Klopp, N., Prochnow, B., Illig, T., Schindler, C., Guzman, C. A. & Pessler, F. 2017. Motivations for (Non)Participation in Population-Based Health Studies among the Elderly – Comparison of Participants and Nonparticipants of a Prospective Study on Influenza Vaccination. *BMC Medical Research Methodology*, 17(1), 1-18.
- Alarhayem, A., Achebe, E. & Logue, A. J. 2015. Psychosocial Support of the Inflammatory Bowel Disease Patient. *Surgical Clinics of North America*, 95(6), 1281-1293.
- Albrecht, T. A. & Taylor, A. G. 2013. No Stone Left Unturned: Challenges Encountered During Recruitment of Women with Advanced Ovarian Cancer for a Phase I Study. *Applied Nursing Research*, 26(4), 245-250.
- Alfadhli, A. A., Mcdonald, J. W. & Feagan, B. G. 2004. Methotrexate for Induction of Remission in Refractory Crohn's Disease. *The Cochrane Database of Systematic Reviews*, 1(4), 003459-3470.
- Ali, S., Matcham, F., Irving, K. & Chalder, T. 2017. Fatigue and Psychosocial Variables in Autoimmune Rheumatic Disease and Chronic Fatigue Syndrome: A Cross-Sectional Comparison. *Journal of Psychosomatic Research*, 92(SC), 1-8.
- Ali, T. & Orr, W. C. 2014. Sleep Disturbances and Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, 20(11), 1986-1995.
- Allez, M., Karmiris, K., Louis, E., Van Assche, G., Ben-Horin, S., Klein, A., Van Der Woude, J., Baert, F., Eliakim, R., Katsanos, K., Brynskov, J., Steinwurz, F., Danese, S., Vermeire, S., Teillaud, J.-L., Lémann, M. & Chowers, Y. 2010. Report of the Ecco Pathogenesis Workshop on Anti-Tnf Therapy Failures in Inflammatory Bowel Diseases: Definitions, Frequency and Pharmacological Aspects. *Journal of Crohn's and Colitis*, 4(4), 355-366.
- Alrubaiy, L., Rikaby, I., Dodds, P., Hutchings, H. A. & Williams, J. G. 2015. Systematic Review of the Health Related Quality of Life (Hrql) Measures for Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 9(3), 284-292.

- Altman, D. G., Schulz, K. F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., Gøtzsche, P. C. & Lang, T. 2001. The Revised Consort Statement for Reporting Randomized Trials: Explanation and Elaboration. *Annals of Internal Medicine*, 134(8), 663-694.
- Amtmann, D., Kim, J., Chung, H., Bamer, A. M., Askew, R. L., Wu, S., Cook, K. F. & Johnson, K. L. 2014. Comparing Cesd-10, Phq-9, and Promis Depression Instruments in Individuals with Multiple Sclerosis. *Rehabilitation Psychology*, 59(2), 220-229.
- Ananthakrishnan, A. N. 2015. Epidemiology and Risk Factors for Ibd. *Nature Reviews Gastroenterology & Hepatology*, 12(4), 205-217.
- Ananthakrishnan, A. N., Bernstein, C. N., Iliopoulos, D., Macpherson, A., Neurath, M. F., Ali, R. a. R., Vavricka, S. R. & Fiocchi, C. 2018. Environmental Triggers in Ibd: A Review of Progress and Evidence. *Nature Reviews Gastroenterology and Hepatology*, 15(1), 39.
- Anderson, L. M., Petticrew, M., Rehfuss, E., Armstrong, R., Ueffing, E., Baker, P., Francis, D. & Tugwell, P. 2011. Using Logic Models to Capture Complexity in Systematic Reviews. *Research Synthesis Methods*, 2(1), 33-42.
- Annese, V., Daperno, M., Rutter, M. D., Amiot, A., Bossuyt, P., East, J., Ferrante, M., Götz, M., Katsanos, K. H. & Kießlich, R. 2013. European Evidence Based Consensus for Endoscopy in Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 7(12), 982-1018.
- Annese, V., Duricova, D., Gower-Rousseau, C., Jess, T. & Langholz, E. 2015. Impact of New Treatments on Hospitalisation, Surgery, Infection, and Mortality in Ibd: A Focus Paper by the Epidemiology Committee of Ecco. *Journal of Crohn's and Colitis*, 10(2), 216-225.
- Anthoine, E., Moret, L., Regnault, A., Sébille, V. & Hardouin, J. B. 2014. Sample Size Used to Validate a Scale: A Review of Publications on Newly-Developed Patient Reported Outcomes Measures. *Health and Quality of Life Outcomes*, 12(1), 176-188.
- Ariyaratnam, J. & Subramanian, V. 2014. Association between Thiopurine Use and Nonmelanoma Skin Cancers in Patients with Inflammatory Bowel Disease: A Meta-Analysis. *The American Journal of Gastroenterology*, 109(2), 163.
- Arnett, S. V. & Clark, I. 2012. Inflammatory Fatigue and Sickness Behaviour—Lessons for the Diagnosis and Management of Chronic Fatigue Syndrome. *Journal of Affective Disorders*, 141(2), 130-142.
- Artom, M., Czubier-Dochan, W., Sturt, J. & Norton, C. 2016. Targets for Health Interventions for Inflammatory Bowel Disease-Fatigue. *Journal of Crohn's and Colitis*, 10(7), 860-869.
- Artom, M., Czubier-Dochan, W., Sturt, J. & Norton, C. 2017. Cognitive Behavioural Therapy for the Management of Inflammatory Bowel Disease-Fatigue with a Nested Qualitative Element: Study Protocol for a Randomised Controlled Trial. *Trials*, 18(1), 213-226.
- Artom, M., Czubier-Dochan, W., Sturt, J., Proudfoot, H., Norton, C. 2018. Cognitive Behavioural Therapy for the Management of Inflammatory Bowel Disease-Fatigue: A Pilot Randomised Controlled Trial. *Submitted*.
- Artom, M., Czubier-Dochan, W., Sturt, J., Murrells, T., Norton, C. 2016 The Contribution of Clinical and Psychosocial Factors in Inflammatory Bowel Disease-Fatigue: A Cross-Sectional Study to Fatigue in 182 Patients with Inflammatory Bowel Disease *Alimentary Pharmacology & Therapeutics*, 43(3), 403-416.

- Attwood, S., Morton, K., Mitchell, J., Van Emmenis, M. & Sutton, S. 2016. Reasons for Non-Participation in a Primary Care-Based Physical Activity Trial: A Qualitative Study. *British Medical Journal Open*, 6(5), e011577.
- Avery, K. N. L., Donovan, J. L., Horwood, J. & Lane, J. A. 2013. Behavior Theory for Dietary Interventions for Cancer Prevention: A Systematic Review of Utilization and Effectiveness in Creating Behavior Change. *Cancer Causes & Control*, 24(3), 409-420.
- Ayling, K., Brierley, S., Johnson, B., Heller, S. & Eiser, C. 2015. Efficacy of Theory-Based Interventions for Young People with Type 1 Diabetes: A Systematic Review and Meta-Analysis. *British Journal of Health Psychology*, 20(2), 428-446.
- Bager, P., Befrits, R., Wikman, O., Lindgren, S., Moum, B., Hjortswang, H. & Dahlerup, J. F. 2011. The Prevalence of Anemia and Iron Deficiency in Ibd Outpatients in Scandinavia. *Scandinavian Journal of Gastroenterology*, 46(3), 304-309.
- Bager P, V. C., Juul T, Dahlerup J.F. 2017. N795 Fatigue in Ibd Must Be to Compared to the Background Population – Generation of Normative Data for the Ibd-F. *Conference Abstract*.
- Bager, P., Vestergaard, C., Juul, T. & Dahlerup, J. 2017. N795 Fatigue in Ibd Must Be to Compared to the Background Population-Generation of Normative Data for the Ibd-F. *Journal of Crohn's & Colitis*, 11(S1), S488-S489.
- Baker, T. B., Gustafson, D. H. & Shah, D. 2014. How Can Research Keep up with Ehealth? Ten Strategies for Increasing the Timeliness and Usefulness of Ehealth Research. *Journal of Medical Internet Research*, 16(2), e36-36.
- Ballesio, A., Aquino, M. R. J. V., Feige, B., Johann, A. F., Kyle, S. D., Spiegelhalder, K., Lombardo, C., Rücker, G., Riemann, D. & Baglioni, C. 2017. The Effectiveness of Behavioural and Cognitive Behavioural Therapies for Insomnia on Depressive and Fatigue Symptoms: A Systematic Review and Network Meta-Analysis. *Sleep Medicine Reviews*, 37(1), 114-129.
- Bannink, F. 2017. Positive Cbt in Practice. *Positive Psychology Interventions in Practice*. Springer.
- Bardhan, K., Simmonds, N., Royston, C., Dhar, A. & Edwards, C. 2010. A United Kingdom Inflammatory Bowel Disease Database: Making the Effort Worthwhile. *Journal of Crohn's and Colitis*, 4(4), 405-412.
- Barley, E. A., Haddad, M., Simmonds, R., Fortune, Z., Walters, P., Murray, J., Rose, D. & Tylee, A. 2012. The Upbeat Depression and Coronary Heart Disease Programme: Using the Uk Medical Research Council Framework to Design a Nurse-Led Complex Intervention for Use in Primary Care. *BMC Family Practice*, 13(1), 119-129.
- Barned, C., Stinzi, A., Mack, D. & O'doherty, K. C. 2016. To Tell or Not to Tell: A Qualitative Interview Study on Disclosure Decisions among Children with Inflammatory Bowel Disease. *Social Science & Medicine*, 162(115-123).
- Bartholomew, L. K., Parcel, G. S. & Kok, G. 1998. Intervention Mapping: A Process for Developing Theory and Evidence-Based Health Education Programs. *Health Education & Behavior*, 25(5), 545-563.

- Battat, R., Kopylov, U., Szilagyi, A., Saxena, A., Rosenblatt, D. S., Warner, M., Bessissow, T., Seidman, E. & Bitton, A. 2014. Vitamin B12 Deficiency in Inflammatory Bowel Disease: Prevalence, Risk Factors, Evaluation, and Management. *Inflammatory Bowel Diseases*, 20(6), 1120-1128.
- Baumgart, D. C. & Sandborn, W. J. 2016. Crohn's Disease. *The Lancet*, 380(9853), 1590-1605.
- Beck, A., Bager, P., Jensen, P. E. & Dahlerup, J. F. 2013. How Fatigue Is Experienced and Handled by Female Outpatients with Inflammatory Bowel Disease. *Gastroenterology Research and Practice*, 2013(1), 1-8.
- Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K. F. & Simel, D. 1996. Improving the Quality of Reporting of Randomized Controlled Trials: The Consort Statement. *Journal of the American Medical Association*, 276(8), 637-639.
- Ben, T. J., Charfi, N., Mnif, L., Yaich, S., Zouari, L., Zouari, N., Tahri, N., Damak, J. & Maalej, M. 2012. Emotional Disorders and Inflammatory Bowel Disease. *La Tunisie Medicale*, 90(7), 557-563.
- Bernstein, C. N. 2015. Treatment of Ibd: Where We Are and Where We Are Going. *The American journal of gastroenterology*, 110(1), 114-126.
- Bernstein, C. N., Rawsthorne, P., Cheang, M. & Blanchard, J. F. 2006a. A Population-Based Case Control Study of Potential Risk Factors for Ibd. *The American Journal of Gastroenterology*, 101(5), 993-1002.
- Bernstein, C. N., Wajda, A., Svenson, L. W., Mackenzie, A., Koehoorn, M., Jackson, M., Fedorak, R., Israel, D. & Blanchard, J. F. 2006b. The Epidemiology of Inflammatory Bowel Disease in Canada: A Population-Based Study. *The American Journal of Gastroenterology*, 101(7), 1559-1568.
- Best, W. R., Beckett, J. M. & Singleton, J. W. 1979. Rederived Values of the Eight Coefficients of the Crohn's Disease Activity Index *Gastroenterology*, 77(4), 843-846.
- Bhurke, S., Cook, A., Tallant, A., Young, A., Williams, E. & Raftery, J. 2015. Using Systematic Reviews to Inform Nihl Trial Planning and Design: A Retrospective Cohort. *BMC Medical Research Methodology*, 15(1), 108-118.
- Bjelland, I., Dahl, A. A., Haug, T. T. & Neckelmann, D. 2002. The Validity of the Hospital Anxiety and Depression Scale: An Updated Literature Review. *Journal of Psychosomatic Research*, 52(2), 69-77.
- Blackwood, B. 2006. Methodological Issues in Evaluating Complex Healthcare Interventions. *Journal of Advanced Nursing*, 54(5), 612-622.
- Blackwood, B., O'halloran, P. & Porter, S. 2010. On the Problems of Mixing Rcts with Qualitative Research: The Case of the Mrc Framework for the Evaluation of Complex Healthcare Interventions. *Journal of Research in Nursing*, 15(6), 511-521.
- Bodger, K., Ormerod, C., Shackcloth, D., Harrison, M., Ahmed, S., Bowering, K., Brown, E., Hurst, A. & Gledhill, T. 2014. Development and Validation of a Rapid, Generic Measure of Disease Control from the Patient's Perspective: The Ibd-Control Questionnaire. *Gut*, 63(7), 1092-1102.
- Bojic, D., Bodger, K. & Travis, S. 2016. Patient Reported Outcome Measures (Proms) in Inflammatory Bowel Disease: New Data. *Journal of Crohn's and Colitis*, 11(S2), S576-S585.

- Bol, Y., Duits, A.A., Vertommen-Mertens, C.E., Hupperts, R.M., Romberg-Camps, M.J., Verhey, F.R. and Vlaeyen, J.W., 2010. The contribution of disease severity, depression and negative affectivity to fatigue in multiple sclerosis: a comparison with ulcerative colitis. *Journal of Psychosomatic Research*, 69(1), 43-49.
- Bombardier, C. H., Richards, J. S., Krause, J. S., Tulskey, D. & Tate, D. G. 2004. Symptoms of Major Depression in People with Spinal Cord Injury: Implications for Screening. *Archives of Physical Medicine and Rehabilitation*, 85(11), 1749-56.
- Bonaz, B. L. & Bernstein, C. N. 2013. Brain-Gut Interactions in Inflammatory Bowel Disease. *Gastroenterology*, 144(1), 36-49.
- Bond, G. R., Evans, L., Salyers, M. P., Williams, J. & Kim, H.-W. 2000. Measurement of Fidelity in Psychiatric Rehabilitation. *Mental Health Services Research*, 2(2), 75-87.
- Bonell, C., Jamal, F., Melendez-Torres, G. & Cummins, S. 2014. 'Dark Logic': Theorising the Harmful Consequences of Public Health Interventions. *Journal of Epidemiology & Community Health*, 69(1), 95-98.
- Bradbury, K., Watts, S., Arden-Close, E., Yardley, L. & Lewith, G. 2014. Developing Digital Interventions: A Methodological Guide. *Evidence-Based Complementary and Alternative Medicine*, 1(1), 1-7.
- Brazier, H. & Begley, C. M. 1996. Selecting a Database for Literature Searches in Nursing: Medline or Cinahl? *Journal of Advanced Nursing*, 24(4), 868-875.
- Brédart, A., Razavi, D., Robertson, C., Brignone, S., Fonzo, D., Petit, J.-Y. & De Haes, J. 2002. Timing of Patient Satisfaction Assessment: Effect on Questionnaire Acceptability, Completeness of Data, Reliability and Variability of Scores. *Patient Education and Counseling*, 46(2), 131-136.
- Brett, J., Staniszewska, S., Mockford, C., Herron-Marx, S., Hughes, J., Tysall, C. & Suleman, R. 2014. Mapping the Impact of Patient and Public Involvement on Health and Social Care Research: A Systematic Review. *Health Expectations*, 17(5), 637-650.
- Broadbent, E., Ellis, C. J., Thomas, J., Gamble, G. & Petrie, K. J. 2009. Further Development of an Illness Perception Intervention for Myocardial Infarction Patients: A Randomized Controlled Trial. *Journal of Psychosomatic Research*, 67(1), 17-23.
- Broadbent, E., Petrie, K. J., Main, J. & Weinman, J. 2006. The Brief Illness Perception Questionnaire. *Journal of Psychosomatic Research*, 60(6), 631-637.
- Broadbent, E., Wilkes, C., Koschwanez, H., Weinman, J., Norton, S. & Petrie, K. J. 2015. A Systematic Review and Meta-Analysis of the Brief Illness Perception Questionnaire. *Psychology & Health*, 30(11), 1361-1385.
- Brown, C. A. & Lilford, R. J. 2006. The Stepped Wedge Trial Design: A Systematic Review. *BMC Medical Research Methodology*, 6(1), 54-63.
- Buell, J. F., Gross, T. G. & Woodle, E. S. 2005. Malignancy after Transplantation. *Transplantation*, 80(2S), S254-S264.
- Burisch, J., Jess, T., Martinato, M. & Lakatos, P. L. 2013. The Burden of Inflammatory Bowel Disease in Europe. *Journal of Crohn's and Colitis*, 7(4), 322-337.

- Burisch, J. & Munkholm, P. 2015. The Epidemiology of Inflammatory Bowel Disease. *Scandinavian Journal of Gastroenterology*, 50(8), 942-951.
- Burisch, J., Pedersen, N., Čuković-Čavka, S., Brinar, M., Kaimakliotis, I., Duricova, D., Shonová, O., Vind, I., Avnstrøm, S. & Thorsgaard, N. 2014. East–West Gradient in the Incidence of Inflammatory Bowel Disease in Europe: The Ecco-Epicom Inception Cohort. *Gut*, 63(4), 588-597.
- Burr J.M., C. M. K., Campbell S.E., Francis J.J., Greene A., Hernández R., Et Al. 2011. Developing the Clinical Components of a Complex Intervention for a Glaucoma Screening Trial: A Mixed Methods Study. *BMC Medical Research Methodology*, 11(1), 54.
- Butler, C. C., Vidal-Alaball, J., Cannings-John, R., Mccaddon, A., Hood, K., Papaioannou, A., McDowell, I. & Goringe, A. 2006. Oral Vitamin B12 Versus Intramuscular Vitamin B12 for Vitamin B12 Deficiency: A Systematic Review of Randomized Controlled Trials. *Family Practice*, 23(3), 279-285.
- Byng, R. & Jones, R. 2004. Mental Health Link: The Development and Formative Evaluation of a Complex Intervention to Improve Shared Care for Patients with Long-Term Mental Illness. *Journal of Evaluation in Clinical Practice*, 10(1), 27-36.
- Byrne, G., Rosenfeld, G., Leung, Y., Qian, H., Raudzus, J., Nunez, C. & Bressler, B. 2017. Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease. *Canadian Journal of Gastroenterology and Hepatology*, 2017(1), 1-6.
- Byrne, M., Cupples, M. E., Smith, S. M., Leathem, C., Corrigan, M., Byrne, M. C. & Murphy, A. W. 2006. Development of a Complex Intervention for Secondary Prevention of Coronary Heart Disease in Primary Care Using the Uk Medical Research Council Framework. *American Journal of Managed Care*, 12(5), 261-266.
- Calloway, A., Dalal, R., Beaulieu, D. B., Duley, C., Annis, K., Gaines, L., Slaughter, C., Schwartz, D. A. & Horst, S. 2017. Depressive Symptoms Predict Anti-Tumor Necrosis Factor Therapy Noncompliance in Patients with Inflammatory Bowel Disease. *Digestive Diseases and Sciences*, 62(12), 3563-3567.
- Calvet, X., Gallardo, O., Coronas, R., Casellas, F., Montserrat, A., Torrejón, A., Vergara, M., Campo, R. & Brullet, E. 2006. Remission on Thiopurinic Immunomodulators Normalizes Quality of Life and Psychological Status in Patients with Crohn's Disease. *Inflammatory Bowel Diseases*, 12(8), 692-696.
- Cambon, L., Minary, L., Ridde, V. & Alla, F. 2012. Transferability of Interventions in Health Education: A Review. *BMC Public Health*, 12(1), 497-510.
- Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P., Spiegelhalter, D. & Tyrer, P. 2000. Framework for Design and Evaluation of Complex Interventions to Improve Health. *British Medical Journal*, 321(7262), 694-696.
- Campbell, N. C., Murray, E., Darbyshire, J., Emery, J., Farmer, A., Griffiths, F., Guthrie, B., Lester, H., Wilson, P. & Kinmonth, A. L. 2007. Designing and Evaluating Complex Interventions to Improve Health Care. *British Medical Journal*, 334(7591), 455-459.
- Cantoro, L., Di Sabatino, A., Papi, C., Margagnoni, G., Ardizzone, S., Giuffrida, P., Giannarelli, D., Massari, A., Monterubbianesi, R., Lenti, M. V., Corazza, G. R. & Kohn, A. 2017. The Time

- Course of Diagnostic Delay in Inflammatory Bowel Disease over the Last Sixty Years: An Italian Multicentre Study. *Journal of Crohn's and Colitis*, 11(8), 975-980.
- Card, T., Hubbard, R. & Logan, R. F. 2003. Mortality in Inflammatory Bowel Disease: A Population-Based Cohort Study. *Gastroenterology*, 125(6), 1583-1590.
- Carnes, D., Homer, K., Underwood, M., Pincus, T., Rahman, A. & Taylor, S. J. 2013. Pain Management for Chronic Musculoskeletal Conditions: The Development of an Evidence-Based and Theory-Informed Pain Self-Management Course. *British Medical Journal Open*, 3(11), e003534.
- Carroll, K. M. & Nuro, K. F. 2002. One Size Cannot Fit All: A Stage Model for Psychotherapy Manual Development. *Clinical Psychology: Science and Practice*, 9(4), 396-406.
- Carter, M. J., Lobo, A. J. & Travis, S. P. 2004. Guidelines for the Management of Inflammatory Bowel Disease in Adults. *Gut*, 53(S5), 1-16.
- Casellas, F., Herrera-De Guise, C., Robles, V., Navarro, E. & Borrueal, N. 2016. Patient Preferences for Inflammatory Bowel Disease Treatment Objectives. *Digestive and Liver Disease*, 49(2), 152-156.
- Casellas, F., Vicens, D. G., Menéndez, S. R. & Oliver, N. A. 2014. Patients' Perceptions, Attitudes, and Experiences About the Management of Mild-to-Moderate Ulcerative Colitis. *Journal of Crohn's and Colitis*, 8(9), 1097-1107.
- Casey, B., Coote, S., Shirazipour, C., Hannigan, A., Motl, R., Ginis, K. M. & Latimer-Cheung, A. 2016. Modifiable Psychosocial Constructs Associated with Physical Activity Participation in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation*, 97(7), 1453-1475.
- Cella, D., Lai, J.-S., Jensen, S. E., Christodoulou, C., Junghaenel, D. U., Reeve, B. B. & Stone, A. A. 2016. Promis Fatigue Item Bank Had Clinical Validity across Diverse Chronic Conditions. *Journal of Clinical Epidemiology*, 73(1), 128-134.
- Cella, D., Peterman, A., Passik, S., Jacobsen, P. & Breitbart, W. 1998. Progress toward Guidelines for the Management of Fatigue. *Oncology*, 12(11A), 369-377.
- Cerrillo, E., Beltrán, B., Pous, S., Echarri, A., Gallego, J. C., Iborra, M., Pamies, J. & Nos, P. 2015. Fecal Calprotectin in Ileal Crohn's Disease: Relationship with Magnetic Resonance Enterography and a Pathology Score. *Inflammatory Bowel Diseases*, 21(7), 1572-1579.
- Chalder, T. & Willis, C. 2017. "Lumping" and "Splitting" Medically Unexplained Symptoms: Is There a Role for a Transdiagnostic Approach? *Journal of Mental Health*, 26(3), 187.
- Chalmers, I., Bracken, M. B., Djulbegovic, B., Garattini, S., Grant, J., Gülmezoglu, A. M., Howells, D. W., Ioannidis, J. P. & Oliver, S. 2014. How to Increase Value and Reduce Waste When Research Priorities Are Set. *The Lancet*, 383(9912), 156-165.
- Chalmers, I. & Glasziou, P. 2009. Avoidable Waste in the Production and Reporting of Research Evidence. *Obstetrics & Gynecology*, 114(6), 1341-1345.
- Chan, A.-W., Song, F., Vickers, A., Jefferson, T., Dickersin, K., Gøtzsche, P. C., Krumholz, H. M., Ghersi, D. & Van Der Worp, H. B. 2014a. Increasing Value and Reducing Waste: Addressing Inaccessible Research. *Lancet*, 383(9913), 257-266.

- Chan, A.-W., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gøtzsche, P. C., Krleža-Jerić, K., Hróbjartsson, A., Mann, H., Dickersin, K. & Berlin, J. A. 2013. Spirit 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine*, 158(3), 200-207.
- Chan, A., Hróbjartsson, A., Haahr, M. T., Gøtzsche, P. C. & Altman, D. G. 2004. Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to Published Articles. *Journal of the American Medical Association*, 291(20), 2457-2465.
- Chan, L., Heinemann, A. W. & Roberts, J. 2014b. Elevating the Quality of Disability and Rehabilitation Research: Mandatory Use of the Reporting Guidelines: Mandatory Use of the Reporting Guidelines. *Pediatric Physical Therapy*, 26(3), 280-282.
- Chande, N., Marshall, J. K., Seow, C. H., Sandborn, W. J., Parker, C. E., Nelson, S. & Feagan, B. G. 2015a. New Applications for Traditional Drugs in Inflammatory Bowel Disease: What Do Cochrane Reviews Tell Us? *Inflammatory bowel diseases*, 21(12), 2948-2957.
- Chande, N., Patton, P. H., Tsoulis, D. J., Thomas, B. S. & Macdonald, J. K. 2015b. Azathioprine or 6-Mercaptopurine for Maintenance of Remission in Crohn's Disease. *The Cochrane Library*.
- Chande, N., Wang, Y., Macdonald, J. K. & McDonald, J. W. 2014. Methotrexate for Induction of Remission in Ulcerative Colitis. *The Cochrane Library*.
- Chaparro, M., Panes, J., García, V., Mañosa, M., Esteve, M., Merino, O., Andreu, M., Gutierrez, A., Gomollón, F. & Cabriada, J. L. 2011. Long-Term Durability of Infliximab Treatment in Crohn's Disease and Efficacy of Dose "Escalation" in Patients Losing Response. *Journal of Clinical Gastroenterology*, 45(2), 113-118.
- Charlesworth, G., Burnell, K., Hoe, J., Orrell, M. & Russell, I. 2013. Acceptance Checklist for Clinical Effectiveness Pilot Trials: A Systematic Approach. *BMC Medical Research Methodology*, 13(1), 78.
- Chervin, R. D. 2003. Epworth Sleepiness Scale? *Sleep Medicine*, 4(3), 175-176.
- Cheung, W.-Y., Garratt, A. M., Russell, I. T. & Williams, J. G. 2000. The Uk Ibdq—a British Version of the Inflammatory Bowel Disease Questionnaire: Development and Validation. *Journal of Clinical Epidemiology*, 53(3), 297-306.
- Chilcot, J. & Moss-Morris, R. 2013. Changes in Illness-Related Cognitions Rather Than Distress Mediate Improvements in Irritable Bowel Syndrome Symptoms and Disability Following a Brief Cognitive Behavioural Therapy Intervention. *Behaviour Research and Therapy*, 51(10), 690-695.
- Chilcot, J., Moss-Morris, R., Artom, M., Harden, L., Picariello, F., Hughes, H., Bates, S. & Macdougall, I. C. 2016. Psychosocial and Clinical Correlates of Fatigue in Haemodialysis Patients: The Importance of Patients' Illness Cognitions and Behaviours. *International Journal of Behavioral Medicine*, 23(3), 271-281.
- Chowers, Y., Sturm, A., Sans, M., Papadakis, K., Gazouli, M., Harbord, M., Jahnel, J., Mantzaris, G. J., Meier, J., Mottet, C., Peyrin-Biroulet, L. & Allez, M. 2010. Report of the Ecco Workshop on Anti-Tnf Therapy Failures in Inflammatory Bowel Diseases: Biological Roles and Effects of Tnf and Tnf Antagonists. *Journal of Crohn's and Colitis*, 4(4), 367-376.

- Ciccocioppo, R., Klersy, C., Russo, M. L., Valli, M., Boccaccio, V., Imbesi, V., Ardizzone, S., Porro, G. B. & Corazza, G. R. 2011. Validation of the Italian Translation of the Inflammatory Bowel Disease Questionnaire. *Digestive and Liver Disease*, 43(7), 535-541.
- Clark, D. M., Layard, R., Smithies, R., Richards, D. A., Suckling, R. & Wright, B. 2009. Improving Access to Psychological Therapy: Initial Evaluation of Two Uk Demonstration Sites. *Behaviour Research and Therapy*, 47(11), 910-920.
- Clark, H. & Anderson, A. A. Theories of Change and Logic Models: Telling Them Apart. American Evaluation Association Conference, 2004 Atlanta.
- Cluydts, R., De Valck, E., Verstraeten, E. & Theys, P. 2002. Daytime Sleepiness and Its Evaluation. *Sleep Medicine Reviews*, 6(2), 83-96.
- Clyne, B., Bradley, M. C., Hughes, C. M., Clear, D., McDonnell, R., Williams, D., Fahey, T. & Smith, S. M. 2013. Addressing Potentially Inappropriate Prescribing in Older Patients: Development and Pilot Study of an Intervention in Primary Care (the Opti-Script Study). *BMC Health Services Research*, 13(1), 307.
- Coates, M., Gorrepati Venkata, S., Navabi, S., Stuart, A., Bobb, A., Koltun, W., Tinsley, A. & Williams, E. 2017. P-096 the Influence of Affective Spectrum Disorders on Symptom Burden within Inflammatory Bowel Disease Populations. *Inflammatory Bowel Diseases*, 23(S1), S36.
- Cohen, B., Zoega, H., Shah, S., Leleiko, N., Lidofsky, S., Bright, R., Flowers, N., Law, M., Moniz, H. & Merrick, M. 2014. Fatigue Is Highly Associated with Poor Health-Related Quality of Life, Disability and Depression in Newly-Diagnosed Patients with Inflammatory Bowel Disease, Independent of Disease Activity. *Alimentary Pharmacology & Therapeutics*, 39(8), 811-822.
- Cohen, S., Kamarck, T. & Mermelstein, R. 1983. A Global Measure of Perceived Stress. *Journal of Health and Social Behavior*, 385-396.
- Colombel, J.-F., Panaccione, R., Bossuyt, P., Lukas, M., Baert, F., Vaňásek, T., Danalioglu, A., Novacek, G., Armuzzi, A., Hébuterne, X., Travis, S., Danese, S., Reinisch, W., Sandborn, W. J., Rutgeerts, P., Hommes, D., Schreiber, S., Neimark, E., Huang, B., Zhou, Q., Mendez, P., Petersson, J., Wallace, K., Robinson, A. M., Thakkar, R. B. & D'haens, G. 2017. Effect of Tight Control Management on Crohn's Disease (Calm): A Multicentre, Randomised, Controlled Phase 3 Trial. *The Lancet*, 390(10114), 2779-2789.
- Colombel, J. F. & Mahadevan, U. 2017. Inflammatory Bowel Disease 2017: Innovations and Changing Paradigms. *Gastroenterology*, 152(2), 309-312.
- Conn, V. S., Algase, D. L., Rowl, S. M., Zerwic, J. J. & Wyman, J. F. 2010. Publishing Pilot Intervention Work. *Western Journal of Nursing Research*, 32(8), 994-1010.
- Connors, J., Basseri, S., Grant, A., Giffin, N., Mahdi, G., Noble, A., Rashid, M., Otley, A. and Van Limbergen, J., 2017. Exclusive enteral nutrition therapy in paediatric crohn's disease results in long-term avoidance of corticosteroids: Results of a propensity-score matched cohort analysis. *Journal of Crohn's and Colitis*, 11(9), 1063-1070.
- Corbett, T., Walsh, J., Groarke, A. & McGuire, B. 2015. Applying the Common Sense Model of Health and Illness Self-Regulation to Perceptions of Persistent Cancer-Related Fatigue after Treatment: A Focus Group Study. *Psycho-Oncology* 24(S2), 248-249.

- Corbett, T., Walsh, J. C., Groarke, A., Moss-Morris, R. & McGuire, B. E. 2016. Protocol for a Pilot Randomised Controlled Trial of an Online Intervention for Post-Treatment Cancer Survivors with Persistent Fatigue. *British Medical Journal Open*, 6(6), e011485.
- Corry, M., Clarke, M., While, A. E. & Lalor, J. 2013. Developing Complex Interventions for Nursing: A Critical Review of Key Guidelines. *Journal of Clinical Nursing*, 22(17-18), 2366-2386.
- Coryn, C. L., Noakes, L. A., Westine, C. D. & Schröter, D. C. 2011. A Systematic Review of Theory-Driven Evaluation Practice from 1990 to 2009. *American Journal of Evaluation*, 32(2), 199-226.
- Cosco, T. D., Doyle, F., Ward, M. & McGee, H. 2012. Latent Structure of the Hospital Anxiety and Depression Scale: A 10-Year Systematic Review. *Journal of Psychosomatic Research*, 72(3), 180-184.
- Cosnes, J., Gower-Rousseau, C., Seksik, P. & Cortot, A. 2011. Epidemiology and Natural History of Inflammatory Bowel Diseases. *Gastroenterology*, 140(6), 1785-1794.
- Costantini, A. & Pala, M. I. 2013. Thiamine and Fatigue in Inflammatory Bowel Diseases: An Open-Label Pilot Study. *The Journal of Alternative and Complementary Medicine*, 19(8), 704-708.
- Craig, P., Dieppe, P. & Macintyre, S. 2008. Developing and Evaluating Complex Interventions: The New Medical Research Council Guidance. *British Medical Journal*, 337(7676), 979-983.
- Craig, P. & Petticrew, M. 2013. Developing and Evaluating Complex Interventions: Reflections on the 2008 Mrc Guidance. *International Journal of Nursing Studies*, 50(5), 585-587.
- Crowe, M., Whitehead, L., Seaton, P., Jordan, J., McCall, C., Maskill, V. & Trip, H. 2017. Qualitative Meta-Synthesis: The Experience of Chronic Pain across Conditions. *Journal of Advanced Nursing*, 73(5), 1004-1016.
- Czuber-Dochan, W. 2015. *Exploring Fatigue in Inflammatory Bowel Disease as Experienced by Individuals - a Descriptive Phenomenological Study*. King's College London.
- Czuber-Dochan, W., Norton, C., Bassett, P., Berliner, S., Bredin, F., Darvell, M., Forbes, A., Gay, M., Nathan, I. & Ream, E. 2014a. Development and Psychometric Testing of Inflammatory Bowel Disease Fatigue (Ibd-F) Patient Self-Assessment Scale. *Journal of Crohn's & Colitis*, 8(11), 1398-1406.
- Czuber-Dochan, W., Norton, C., Bredin, F., Darvell, M., Nathan, I. & Terry, H. 2014b. Healthcare Professionals' Perceptions of Fatigue Experienced by People with Ibd. *Journal of Crohn's and Colitis*, 8(8), 835-844.
- Czuber-Dochan, W., Ream, E. & Norton, C. 2013a. Review Article: Description and Management of Fatigue in Inflammatory Bowel Disease. *Alimentary Pharmacology & Therapeutics*, 37(5), 505-516.
- Czuber-Dochan, W., Terry, H., Dibley, L. B., Ream, E. & Norton, C. 2013b. The Experience of Fatigue in People with Inflammatory Bowel Disease: An Exploratory Study. *Journal of Advanced Nursing*, 69(9), 1987-1999.
- D'haens, G. R., Sartor, R. B., Silverberg, M. S., Petersson, J. & Rutgeerts, P. 2014. Future Directions in Inflammatory Bowel Disease Management. *Journal of Crohn's and Colitis*, 8(8), 726-734.

- Danese, S., Vuitton, L. & Peyrin-Biroulet, L. 2015. Biologic Agents for Ibd: Practical Insights. *Nature Reviews Gastroenterology & Hepatology*, 12(9), 537-549.
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. & Kelley, K. W. 2008. From Inflammation to Sickness and Depression: When the Immune System Subjugates the Brain. *Nature Reviews Neuroscience*, 9(1), 46-56.
- Datta, J. & Petticrew, M. 2013. Challenges to Evaluating Complex Interventions: A Content Analysis of Published Papers. *BMC Public Health*, 13(1), 568.
- Davies, P., Walker, A. E. & Grimshaw, J. M. 2010. A Systematic Review of the Use of Theory in the Design of Guideline Dissemination and Implementation Strategies and Interpretation of the Results of Rigorous Evaluations. *Implementation Science*, 5(1), 14-20.
- Davis, R., Campbell, R., Hildon, Z., Hobbs, L. & Michie, S. 2015. Theories of Behaviour and Behaviour Change across the Social and Behavioural Sciences: A Scoping Review. *Health Psychology Review*, 9(3), 323-344.
- Dear, B. F., Titov, N., Sunderland, M., Mcmillan, D., Anderson, T., Lorian, C. & Robinson, E. 2011. Psychometric Comparison of the Generalized Anxiety Disorder Scale-7 and the Penn State Worry Questionnaire for Measuring Response During Treatment of Generalised Anxiety Disorder. *Cognitive Behaviour Therapy*, 40(3), 216-227.
- Deary, V., Chalder, T. & Sharpe, M. 2007. The Cognitive Behavioural Model of Medically Unexplained Symptoms: A Theoretical and Empirical Review. *Clinical Psychology Review*, 27(7), 781-797.
- Delgadillo, J., Mcmillan, D., Lucock, M., Leach, C., Ali, S. & Gilbody, S. 2014. Early Changes, Attrition, and Dose-Response in Low Intensity Psychological Interventions. *British Journal of Clinical Psychology*, 53(1), 114-130.
- Dennick, K., Sturt, J. & Speight, J. 2017. What Is Diabetes Distress and How Can We Measure It? A Narrative Review and Conceptual Model. *Journal of Diabetes and its Complications*, 5(31), 898-911.
- Derijks, L., Gilissen, L., Hooymans, P. & Hommes, D. 2006. Review Article: Thiopurines in Inflammatory Bowel Disease. *Alimentary Pharmacology & Therapeutics*, 24(5), 715-729.
- Devlen, J., Beusterien, K., Yen, L., Ahmed, A., Cheifetz, A. S. & Moss, A. C. 2014. The Burden of Inflammatory Bowel Disease: A Patient-Reported Qualitative Analysis and Development of a Conceptual Model. *Inflammatory Bowel Diseases*, 20(3), 545.
- Dibley, L., Bager, P., Czuber-Dochan, W., Farrell, D., Jelsness-Jørgensen, L.-P., Kemp, K. & Norton, C. 2017. Identification of Research Priorities for Inflammatory Bowel Disease Nursing in Europe: A Nurses-European Crohn's and Colitis Organisation Delphi Survey. *Journal of Crohn's and Colitis*, 11(3), 353-359.
- Dickens, C., McGowan, L., Clark-Carter, D. & Creed, F. 2002. Depression in Rheumatoid Arthritis: A Systematic Review of the Literature with Meta-Analysis. *Psychosomatic Medicine*, 64(1), 52-60.
- Dignass, A., Eliakim, R., Magro, F., Maaser, C., Chowers, Y., Geboes, K., Mantzaris, G., Reinisch, W., Colombel, J.-F. & Vermeire, S. 2012. Second European Evidence-Based Consensus on the Diagnosis and Management of Ulcerative Colitis Part 1: Definitions and Diagnosis. *Journal of Crohn's and Colitis*, 6(10), 965-990.

- Dipietro, N. A. 2010. Methods in Epidemiology: Observational Study Designs. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 30(10), 973-984.
- Dittner, A. J., Wessely, S. C. & Brown, R. G. 2004. The Assessment of Fatigue: A Practical Guide for Clinicians and Researchers. *Journal of Psychosomatic Research*, 56(2), 157-170.
- Djurisic, S., Rath, A., Gaber, S., Garattini, S., Bertele, V., Ngwabyt, S.-N., Hivert, V., Neugebauer, E. A., Laville, M. & Hiesmayr, M. 2017. Barriers to the Conduct of Randomised Clinical Trials within All Disease Areas. *Trials*, 18(1), 360.
- Donkin, L. & Glozier, N. 2012. Motivators and Motivations to Persist with Online Psychological Interventions: A Qualitative Study of Treatment Completers. *Journal of Medical Internet Research*, 14(3), e91.
- Donovan, K. A., Small, B. J., Andrykowski, M. A., Munster, P. & Jacobsen, P. B. 2007. Utility of a Cognitive-Behavioral Model to Predict Fatigue Following Breast Cancer Treatment. *Health Psychology*, 26(4), 464-472.
- Dorrian, A., Dempster, M. & Adair, P. 2009. Adjustment to Inflammatory Bowel Disease: The Relative Influence of Illness Perceptions and Coping. *Inflammatory Bowel Diseases*, 15(1), 47-55.
- Downing, A. 2006. Discourse Markers, Pragmatic Markers, Stance Markers. *A Survey in Usos Sociales del Lenguaje y Aspectos Psicolingüísticos*, 1(1), 59-76.
- Dubinsky, M. C. 2004. Azathioprine, 6-Mercaptopurine in Inflammatory Bowel Disease: Pharmacology, Efficacy, and Safety. *Clinical Gastroenterology and Hepatology*, 2(9), 731-743.
- Eady, A. M., Wilczynski, N. L., Haynes, R. B. & For the Hedges, T. 2008. Psycinfo Search Strategies Identified Methodologically Sound Therapy Studies and Review Articles for Use by Clinicians and Researchers. *Journal of Clinical Epidemiology*, 61(1), 34-40.
- Eccles, M., Grimshaw, J., Walker, A., Johnston, M. & Pitts, N. 2005. Changing the Behavior of Healthcare Professionals: The Use of Theory in Promoting the Uptake of Research Findings. *Journal of Clinical Epidemiology*, 58(2), 107-112.
- Egger, M., Juni, P., Bartlett, C., Holenstein, F. & Sterne, J. 2002. How Important Are Comprehensive Literature Searches and the Assessment of Trial Quality in Systematic Reviews? Empirical Study. *Health Technology Assessment*, 7(1), 1-76.
- Eilertsen, G., Ormstad, H., Kirkevold, M., Mengshoel, A.M., Söderberg, S. & Olsson, M., 2015. Similarities and differences in the experience of fatigue among people living with fibromyalgia, multiple sclerosis, ankylosing spondylitis and stroke. *Journal of Clinical Nursing*, 24(13-14), 2023-2034.
- Ekblom, A. 2004. The Epidemiology of Ibd: A Lot of Data but Little Knowledge. How Shall We Proceed? *Inflammatory Bowel Diseases*, 10(S1), 32-34.
- Ettema, R., Schuurmans, M. J., Schutijser, B., Van Baar, M., Kamphof, N. & Kalkman, C. J. 2015. Feasibility of a Nursing Intervention to Prepare Frail Older Patients for Cardiac Surgery: A Mixed-Methods Study. *European Journal of Cardiovascular Nursing*, 14(4), 342-351.

- Ettema, R. G., Hoogendoorn, M. E., Kalkman, C. J. & Schuurmans, M. J. 2014. Development of a Nursing Intervention to Prepare Frail Older Patients for Cardiac Surgery (the Predocs Programme), Following Phase One of the Guidelines of the Medical Research Council. *European Journal of Cardiovascular Nursing*, 13(6), 494-505.
- Evertsz, F. B., Thijssens, N., Stokkers, P., Grootenhuis, M., Bockting, C., Nieuwkerk, P. & Sprangers, M. 2012. Do Inflammatory Bowel Disease Patients with Anxiety and Depressive Symptoms Receive the Care They Need? *Journal of Crohn's and Colitis*, 6(1), 68-76.
- Faes, M. C., Reelick, M. F., Esselink, R. A. & Rikkert, M. G. O. 2010. Developing and Evaluating Complex Healthcare Interventions in Geriatrics: The Use of the Medical Research Council Framework Exemplified on a Complex Fall Prevention Intervention. *Journal of the American Geriatrics Society*, 58(11), 2212-2221.
- Fardet, L., Kassar, A., Cabane, J. & Flahault, A. 2007. Corticosteroid-Induced Adverse Events in Adults. *Drug Safety*, 30(10), 861-881.
- Farquhar, M. C., Ewing, G. & Booth, S. 2011. Using Mixed Methods to Develop and Evaluate Complex Interventions in Palliative Care Research. *Palliative Medicine*, 25(8), 748-757.
- Farr, J. N., Jenkins, J. J. & Paterson, D. G. 1951. Simplification of Flesch Reading Ease Formula. *Journal of Applied Psychology*, 35(5), 333.
- Farrell, D., McCarthy, G. & Savage, E. 2015a. Self-Reported Symptom Burden in Individuals with Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 10(3), 315-322.
- Farrell, D., Savage, E., Norton, C., Jelsness-Jørgensen, L. P., Czuber-Dochan, W. & Artom, M. 2015b. Interventions for Fatigue in Inflammatory Bowel Disease. *The Cochrane Library*, CD012005(12), 1-12.
- Feagan, B. G., Rutgeerts, P., Sands, B. E., Hanauer, S., Colombel, J.-F., Sandborn, W. J., Van Assche, G., Axler, J., Kim, H.-J. & Danese, S. 2013. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *New England Journal of Medicine*, 369(8), 699-710.
- Feagan, B. G., Sandborn, W. J., Gasink, C., Jacobstein, D., Lang, Y., Friedman, J. R., Blank, M. A., Johanss, J., Gao, L.-L., Miao, Y., Adedokun, O. J., Sands, B. E., Hanauer, S. B., Vermeire, S., Targan, S., Ghosh, S., De Villiers, W. J., Colombel, J.-F., Tulassay, Z., Seidler, U., Salzberg, B. A., Desreumaux, P., Lee, S. D., Loftus, E. V. J., Dieleman, L. A., Katz, S. & Rutgeerts, P. 2016. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England Journal of Medicine*, 375(20), 1946-1960.
- Feagins, L. A. & Kane, S. V. 2009. Sexual and Reproductive Issues for Men with Inflammatory Bowel Disease. *The American journal of gastroenterology*, 104(3), 768-773.
- Ferreiro-Iglesias, R., Barreiro-De Acosta, M., Santiago, M. O., Gonzalez, A. L., De La Peña, C. A., Estevez, A. J. B. & Dominguez-Muñoz, J. E. 2016. Fecal Calprotectin as Predictor of Relapse in Patients with Inflammatory Bowel Disease under Maintenance Infliximab Therapy. *Journal of Clinical Gastroenterology*, 50(2), 147-151.
- Fewtrell, M. S., Domellöf, M., Hojsak, I., Hulst, J. M., Kennedy, K., Koletzko, B., Mihatsch, W. & Stijnen, T. 2016. Attrition in Long-Term Nutrition Research Studies: A Commentary by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Early Nutrition Research Working Group. *Journal of Pediatric Gastroenterology and Nutrition*, 62(1), 180-182.

- Finlay, L. & Gough, B. 2008. *Reflexivity: A Practical Guide for Researchers in Health and Social Sciences*, John Wiley & Sons.
- Fletcher, A., Jamal, F., Moore, G., Evans, R. E., Murphy, S. & Bonell, C. 2016. Realist Complex Intervention Science: Applying Realist Principles across All Phases of the Medical Research Council Framework for Developing and Evaluating Complex Interventions. *Evaluation*, 22(3), 286-303.
- Freedland, K. E., Mohr, D. C., Davidson, K. W. & Schwartz, J. E. 2011. Usual and Unusual Care: Existing Practice Control Groups in Randomized Controlled Trials of Behavioral Interventions. *Psychosomatic Medicine*, 73(4), 323.
- French, S. D., Green, S. E., O'connor, D. A., Mckenzie, J. E., Francis, J. J., Michie, S., Buchbinder, R., Schattner, P., Spike, N. & Grimshaw, J. M. 2012. Developing Theory-Informed Behaviour Change Interventions to Implement Evidence into Practice: A Systematic Approach Using the Theoretical Domains Framework. *Implementation Science*, 7(1), 38.
- Friedman, L. M., Furberg, C., Demets, D. L., Reboussin, D. M. & Granger, C. B. 1998. *Fundamentals of Clinical Trials*, Springer.
- Frolkis, A. D., Dykeman, J., Negrón, M. E., Jette, N., Fiest, K. M., Frolkis, T., Barkema, H. W., Rioux, K. P., Panaccione, R. & Ghosh, S. 2013. Risk of Surgery for Inflammatory Bowel Diseases Has Decreased over Time: A Systematic Review and Meta-Analysis of Population-Based Studies. *Gastroenterology*, 145(5), 996-1006.
- Gainforth, H. L., West, R. & Michie, S. 2015. Assessing Connections between Behavior Change Theories Using Network Analysis. *Annals of Behavioral Medicine*, 49(5), 754-761.
- Gandhi, S., Jedel, S., Hood, M., Mutlu, E., Swanson, G. & Keshavarzian, A. 2014. The Relationship between Coping, Health Competence and Patient Participation among Patients with Inactive Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 8(5), 401-408.
- Garcia-Vega, E. & Fernandez-Rodriguez, C. 2004. A Stress Management Programme for Crohn's Disease. *Behaviour Research and Therapy*, 42(4), 367-383.
- Gargon, E., Williamson, P. R. & Clarke, M. 2015. Collating the Knowledge Base for Core Outcome Set Development: Developing and Appraising the Search Strategy for a Systematic Review. *BMC Medical Research Methodology*, 15(1), 26.
- Gearry, R. B., Barclay, M. L., Burt, M. J., Collett, J. A. & Chapman, B. A. 2004. Thiopurine Drug Adverse Effects in a Population of New Zealand Patients with Inflammatory Bowel Disease. *Pharmacoepidemiology and Drug Safety*, 13(8), 563-567.
- Gecse, K. B., Khanna, R., Van Den Brink, G. R., Ponsioen, C. Y., Löwenberg, M., Jairath, V., Travis, S. P. L., Sandborn, W. J., Feagan, B. G. & D'haens, G. R. a. M. 2013. Biosimilars in Ibd: Hope or Expectation? *Gut*, 62(6), 803-810.
- Gielissen, M. F., Knoop, H., Servaes, P., Kalkman, J. S., Huibers, M. J., Verhagen, S. & Bleijenberg, G. 2007. Differences in the Experience of Fatigue in Patients and Healthy Controls: Patients' Descriptions. *Health and Quality of Life Outcomes*, 5(1), 36.
- Gielissen, M. F., Verhagen, S., Witjes, F. & Bleijenberg, G. 2006. Effects of Cognitive Behavior Therapy in Severely Fatigued Disease-Free Cancer Patients Compared with Patients Waiting for Cognitive

- Behavior Therapy: A Randomized Controlled Trial. *Journal of Clinical Oncology*, 24(30), 4882-4887.
- Giles, T., Lasserson, T., Smith, B., White, J., Wright, J. & Cates, C. 2006. Continuous Positive Airways Pressure for Obstructive Sleep Apnoea in Adults. *The Cochrane Database of Systematic Reviews*.
- Gisbert, J. P., Marín, A. C. & Chaparro, M. 2016. The Risk of Relapse after Anti-Tnf Discontinuation in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *The American Journal of Gastroenterology*, 111(5), 632-647.
- Gisbert, J. P. & Panés, J. 2009. Loss of Response and Requirement of Infliximab Dose Intensification in Crohn's Disease. *American Journal of Gastroenterology*, 104(3), 760-767.
- Glanz, K. & Bishop, D. B. 2010. The Role of Behavioral Science Theory in Development and Implementation of Public Health Interventions. *Annual Review of Public Health*, 4(31), 399-418
- Glasgow, R. E. & Emmons, K. M. 2007. How Can We Increase Translation of Research into Practice? Types of Evidence Needed. *Annual Review of Public Health*, 28(1), 413-433.
- Glasgow, R. E., Vinson, C., Chambers, D., Khoury, M. J., Kaplan, R. M. & Hunter, C. 2012. National Institutes of Health Approaches to Dissemination and Implementation Science: Current and Future Directions. *American Journal of Public Health*, 102(7), 1274-81.
- Glasgow, R. E., Vogt, T. M. & Boles, S. M. 1999. Evaluating the Public Health Impact of Health Promotion Interventions: The Re-Aim Framework. *American Journal of Public Health*, 89(9), 1322-1327.
- Glasziou, P., Meats, E., Heneghan, C. & Shepperd, S. 2008. What Is Missing from Descriptions of Treatment in Trials and Reviews? *British Medical Journal*, 336(7659), 1472-1474.
- Goedendorp, M. M., Peters, M. E., Gielissen, M. F., Witjes, J. A., Leer, J. W., Verhagen, C. A. & Bleijenberg, G. 2010. Is Increasing Physical Activity Necessary to Diminish Fatigue During Cancer Treatment? Comparing Cognitive Behavior Therapy and a Brief Nursing Intervention with Usual Care in a Multicenter Randomized Controlled Trial. *The Oncologist*, 15(10), 1122-1132.
- Goldenberg, B. A., Graff, L. A., Clara, I., Zarychanski, R., Walker, J. R., Carr, R., Rogala, L., Miller, N. & Bernstein, C. N. 2013. Is Iron Deficiency in the Absence of Anemia Associated with Fatigue in Inflammatory Bowel Disease? *The American Journal of Gastroenterology*, 108(9), 1392-1397.
- Goodhand, J., Kamperidis, N., Sirwan, B., Macken, L., Tshuma, N., Koodun, Y., Chowdhury, F., Croft, N., Direkze, N. & Langmead, L. 2013. Factors Associated with Thiopurine Non-Adherence in Patients with Inflammatory Bowel Disease. *Alimentary Pharmacology & Therapeutics*, 38(9), 1097-1108.
- Goodhand, J., Rampton, D., Joshi, N., Karim, A., Koodun, Y., Macken, L., Baraket, F., Epstein, J., Fell, J. & Ward, D. 2016. Pth-066 Clinical Trial: Effects of Oral Ferrous Sulphate on Haemoglobin, Hepcidin, Disease Activity, Mood and Quality of Life in Adolescents and Adults with Iron Deficiency Anaemia Due to Ibd. *Gut*, 65(S1), A251-A251.
- Goodhand, J., Wahed, M., Mawdsley, J., Farmer, A., Aziz, Q. & Rampton, D. 2012. Mood Disorders in Inflammatory Bowel Disease: Relation to Diagnosis, Disease Activity, Perceived Stress, and Other Factors. *Inflammatory bowel diseases*, 18(12), 2301-2309.

- Gracie, D. J., Irvine, A. J., Sood, R., Mikocka-Walus, A., Hamlin, P. J. & Ford, A. C. 2017. Effect of Psychological Therapy on Disease Activity, Psychological Comorbidity, and Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *The Lancet Gastroenterology & Hepatology*, 2(3), 189-199.
- Gracie, D. J., Williams, C. J., Sood, R., Mumtaz, S., Bholah, M. H., Hamlin, P. J. & Ford, A. C. 2016. Poor Correlation between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. *The American Journal of Gastroenterology*, 111(4), 541-555.
- Graff, L. A., Clara, I., Walker, J. R., Lix, L., Carr, R., Miller, N., Rogala, L. & Bernstein, C. N. 2013. Changes in Fatigue over 2 Years Are Associated with Activity of Inflammatory Bowel Disease and Psychological Factors. *Clinical Gastroenterology and Hepatology*, 11(9), 1140-1146.
- Graff, L. A., Walker, J. R. & Bernstein, C. N. 2009. Depression and Anxiety in Inflammatory Bowel Disease: A Review of Comorbidity and Management. *Inflammatory Bowel Diseases*, 15(7), 1105-1118.
- Gray, C. M., Hunt, K., Mutrie, N., Anderson, A. S., Leishman, J., Dalgarno, L. & Wyke, S. 2013. Football Fans in Training: The Development and Optimization of an Intervention Delivered through Professional Sports Clubs to Help Men Lose Weight, Become More Active and Adopt Healthier Eating Habits. *BMC Public Health*, 13(1), 232-234.
- Green, L. & Kreuter, M. 1999. The Precede–Proceed Model. *Health promotion planning: An educational and environmental approach*, 32-43.
- Grégoire, G., Derderian, F. & Le Lorier, J. 1995. Selecting the Language of the Publications Included in a Meta-Analysis: Is There a Tower of Babel Bias? *Journal of Clinical Epidemiology*, 48(1), 159-163.
- Griffiths, K. M., Farrer, L. & Christensen, H. 2010. The Efficacy of Internet Interventions for Depression and Anxiety Disorders: A Review of Randomised Controlled Trials. *Medical Journal of Australia*, 192(11), S4.
- Griffiths, P. & Riddington, L. 2001. Nurses' Use of Computer Databases to Identify Evidence for Practice—a Cross-Sectional Questionnaire Survey in a Uk Hospital. *Health Information & Libraries Journal*, 18(1), 2-9.
- Grimshaw, J., Thomas, R., Maclennan, G., Fraser, C., Ramsay, C., Vale, L., Whitty, P., Eccles, M., Matowe, L. & Shirran, L. 2005. Effectiveness and Efficiency of Guideline Dissemination and Implementation Strategies. *International Journal of Technology Assessment in Health Care*, 21(01), 149-149.
- Gunesh, S., Thomas, G., Williams, G., Roberts, A. & Hawthorne, A. 2008. The Incidence of Crohn's Disease in Cardiff over the Last 75 Years: An Update for 1996–2005. *Alimentary Pharmacology & Therapeutics*, 27(3), 211-219.
- Guyatt, G., Mitchell, A., Irvine, E. J., Singer, J., Williams, N., Goodacre, R. & Tompkins, C. 1989. A New Measure of Health Status for Clinical Trials in Inflammatory Bowel Disease. *Gastroenterology*, 96(3), 804-810.
- Hagger, M., Koch, S., Chatzisarantis, N. & Orbell, S. 2017. The Common Sense Model of Self-Regulation: Meta-Analysis and Test of a Process Model. *Psychological Bulletin*, 143(11), 1117.

- Hagger, M. S. & Orbell, S. 2003. A Meta-Analytic Review of the Common-Sense Model of Illness Representations. *Psychology & Health*, 18(2), 141-184.
- Haji, F. A., Da Silva, C., Daigle, D. T. & Dubrowski, A. 2014. From Bricks to Buildings: Adapting the Medical Research Council Framework to Develop Programs of Research in Simulation Education and Training for the Health Professions. *Simulation in Healthcare*, 9(4), 249-259.
- Halme, L., Paavola-Sakki, P., Turunen, U., Lappalainen, M., Farkkila, M. & Kontula, K. 2006. Family and Twin Studies in Inflammatory Bowel Disease. *World Journal of Gastroenterology*, 12(23), 3668.
- Han, C. J., Heitkemper, M. M. & Jarrett, M. E. 2016. Fatigue Measures in Noncancer Gastrointestinal Disorders: A Critical Review. *Gastroenterology Nursing*, 39(6), 443-456.
- Han, S. W., Mccoll, E., Barton, J. R., James, P., Steen, I. N. & Welfare, M. R. 2005. Predictors of Quality of Life in Ulcerative Colitis. The Importance of Symptoms and Illness Representations. *Inflammatory Bowel Diseases*, 11(1), 24-34.
- Hanauer, S. 2002. New Steroids for Ibd: Progress Report. *Gut*, 51(2), 182-183.
- Hanauer, S. B. & Sandborn, W. 2001. Management of Crohn's Disease in Adults. *The American Journal of Gastroenterology*, 96(3), 635.
- Hardeman, W., Sutton, S., Griffin, S., Johnston, M., White, A., Wareham, N. J. & Kinmonth, A. L. 2005. A Causal Modelling Approach to the Development of Theory-Based Behaviour Change Programmes for Trial Evaluation. *Health Education Research*, 20(6), 676-687.
- Harries, A. D., Baird, A. & Rhodes, J. 1982. Non-Smoking: A Feature of Ulcerative Colitis. *British Medical Journal*, 284(6317), 706-706.
- Hart, A. L., Lomer, M., Verjee, A., Kemp, K., Faiz, O., Daly, A., Solomon, J. & Mclaughlin, J. 2016. What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease? A Priority Setting Partnership with the James Lind Alliance. *Journal of Crohn's and Colitis*, 11(2), 204-211.
- Hartling, L., Featherstone, R., Nuspl, M., Shave, K., Dryden, D. M. & Vandermeer, B. 2016. The Contribution of Databases to the Results of Systematic Reviews: A Cross-Sectional Study. *BMC Medical Research Methodology*, 16(1), 127.
- Harvey, A. G. 2004. *Cognitive Behavioural Processes across Psychological Disorders: A Transdiagnostic Approach to Research and Treatment*, Oxford University Press, USA.
- Harvey, R. & Bradshaw, J. 1980. A Simple Index of Crohn's-Disease Activity. *The Lancet*, 315(8167), 514.
- Hashash, J. G., Ramos-Rivers, C., Youk, A., Chiu, W. K., Duff, K., Regueiro, M., Binion, D. G., Koutroubakis, I., Vachon, A. & Benhayon, D. 2017. Quality of Sleep and Coexistent Psychopathology Have Significant Impact on Fatigue Burden in Patients with Inflammatory Bowel Disease. *Journal of Clinical Gastroenterology*, 00(00), 1-8.
- Havill, N. L., Leeman, J., Shaw-Kokot, J., Knafl, K., Crandell, J. & Sandelowski, M. 2014. Managing Large-Volume Literature Searches in Research Synthesis Studies. *Nursing Outlook*, 62(2), 112-118.

- Hawe, P. 2015. Minimal, Negligible and Negligent Interventions. *Social Science & Medicine*, 138(SC), 265-268.
- Hawkins, R. P., Kreuter, M., Resnicow, K., Fishbein, M. & Dijkstra, A. 2008. Understanding Tailoring in Communicating About Health. *Health Education Research*, 23(3), 454-466.
- Heine, M., Van Den Akker, L. E., Blikman, L., Hoekstra, T., Van Munster, E., Verschuren, O., Visser-Meily, A. & Kwakkel, G. 2016. Real-Time Assessment of Fatigue in Patients with Multiple Sclerosis: How Does It Relate to Commonly Used Self-Report Fatigue Questionnaires? *Archives of Physical Medicine and Rehabilitation*, 97(11), 1887-1894.
- Hewlett, S., Ambler, N., Almeida, C., Cliss, A., Hammond, A., Kitchen, K., Knops, B., Pope, D., Spears, M. & Swinkels, A. 2011. Self-Management of Fatigue in Rheumatoid Arthritis: A Randomised Controlled Trial of Group Cognitive-Behavioural Therapy. *Annals of the Rheumatic Diseases*, 70(6), 1060-1067.
- Higgins, J. P. & Green, S. 2011. *Cochrane Handbook for Systematic Reviews of Interventions*, John Wiley & Sons.
- Higgins, P. D., Schwartz, M., Mapili, J. & Zimmermann, E. M. 2005. Is Endoscopy Necessary for the Measurement of Disease Activity in Ulcerative Colitis? *The American Journal of Gastroenterology*, 100(2), 355-361.
- Hindryckx, P., Baert, F., Hart, A., Magro, F., Armuzzi, A. & Peyrin-Biroulet, L. 2015. Clinical Trials in Ulcerative Colitis: A Historical Perspective. *Journal of Crohn's and Colitis*, 9(7), 580-588.
- Hjollund, N. H., Andersen, J. H. & Bech, P. 2007. Assessment of Fatigue in Chronic Disease: A Bibliographic Study of Fatigue Measurement Scales. *Health and Quality of Life Outcomes*, 5(1), 12.
- Hoddinott, P. 2015. A New Era for Intervention Development Studies. *Pilot and Feasibility Studies*, 1(1), 36.
- Hoffmann, T., English, T. & Glasziou, P. 2014a. Reporting of Interventions in Randomised Trials: An Audit of Journal Instructions to Authors. *Trials*, 15(1), 20.
- Hoffmann, T., Glasziou, P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D., Barbour, V., Macdonald, H. & Johnston, M. 2014b. Better Reporting of Interventions: Template for Intervention Description and Replication (Tidier) Checklist and Guide. *British Medical Journal*, 348(1), 1687.
- Hoffmann, T. C., Eructi, C. & Glasziou, P. P. 2013. Poor Description of Non-Pharmacological Interventions: Analysis of Consecutive Sample of Randomised Trials. *British Medical Journal*, 347(1), 3755.
- Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D. G., Barbour, V., Macdonald, H. & Johnston, M. 2014c. Better Reporting of Interventions: Template for Intervention Description and Replication (Tidier) Checklist and Guide. *British Medical Journal*, 348(1), 1687.
- Hopkins, C. W. 2017. Inflammatory Bowel Disease, the Hospital Anxiety and Depression Scale and Criterion Contamination. *Inflammatory Bowel Diseases*, 23(11), E54.

- Horsley, T., Dingwall, O. & Sampson, M. 2011. Checking Reference Lists to Find Additional Studies for Systematic Reviews. *The Cochrane Library*.
- Horst, S., Chao, A., Rosen, M., Nohl, A., Duley, C., Wagnon, J. H., Beaulieu, D. B., Taylor, W., Gaines, L. & Schwartz, D. A. 2015. Treatment with Immunosuppressive Therapy May Improve Depressive Symptoms in Patients with Inflammatory Bowel Disease. *Digestive Diseases and Sciences*, 60(2), 465-470.
- Hou, J. K., Gasche, C., Drazin, N. Z., Weaver, S. A., Ehrlich, O. G., Oberai, R., Zapala, S., Siegel, C. A. & Melmed, G. 2016. Assessment of Gaps in Care and the Development of a Care Pathway for Anemia in Patients with Inflammatory Bowel Diseases. *Inflammatory Bowel Diseases*, 23(1), 35-43.
- Huppertz-Hauss, G., Høivik, M. L., Jelsness-Jørgensen, L.-P., Opheim, R., Henriksen, M., Høie, O., Hovde, Ø., Kempski-Monstad, I., Solberg, I. C. & Jahnsen, J. 2017. Fatigue in a Population-Based Cohort of Patients with Inflammatory Bowel Disease 20 Years after Diagnosis: The Ibsen Study. *Scandinavian Journal of Gastroenterology*, 52(3), 351-358.
- Hurley, D. A., Murphy, L. C., Hayes, D., Hall, A. M., Toomey, E., Mcdonough, S. M., Lonsdale, C., Walsh, N. E., Guerin, S. & Matthews, J. 2016. Using Intervention Mapping to Develop a Theory-Driven, Group-Based Complex Intervention to Support Self-Management of Osteoarthritis and Low Back Pain (Solus). *Implementation Science*, 11(1), 56.
- Hyphantis, T., Antoniou, K., Tomenson, B., Tsianos, E., Mavreas, V. & Creed, F. 2010. Is the Personality Characteristic “Impulsive Sensation Seeking” Correlated to Differences in Current Smoking between Ulcerative Colitis and Crohn's Disease Patients? *General Hospital Psychiatry*, 32(1), 57-65.
- Ibd Standards Working Group. 2013. *Ibd Standards: Standards for the Healthcare of People Who Have Inflammatory Bowel Disease (Ibd)* [Online]. London. Available: http://www.ibdstandards.org.uk/uploaded_files/ibdstandards.pdf.
- Iglesias-Rey, M., Barreiro-De Acosta, M., Caamaño-Isorna, F., Rodríguez, I. V., Ferreira, R., Lindkvist, B., González, A. L. & Dominguez-Munoz, J. 2014. Psychological Factors Are Associated with Changes in the Health-Related Quality of Life in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, 20(1), 92-102.
- Irvine, E. J., Feagan, B., Rochon, J., Archambault, A., Fedorak, R. N., Groll, A., Kinnear, D., Saibil, F., Mcdonald, J. W. & Group, C. C. S. R. P. T. S. 1994. Quality of Life: A Valid and Reliable Measure of Therapeutic Efficacy in the Treatment of Inflammatory Bowel Disease. *Gastroenterology*, 106(2), 287-296.
- Jess, T., Lopez, A., Andersson, M., Beaugerie, L. & Peyrin-Biroulet, L. 2014. Thiopurines and Risk of Colorectal Neoplasia in Patients with Inflammatory Bowel Disease: A Meta-Analysis. *Clinical Gastroenterology and Hepatology*, 12(11), 1793-1800.
- Jeuring, S. F., Van Den Heuvel, T. R., Zeegers, M. P., Hameeteman, W. H., Romberg-Camps, M. J., Oostenbrug, L. E., Masclee, A. A., Jonkers, D. M. & Pierik, M. J. 2016. Epidemiology and Long-Term Outcome of Inflammatory Bowel Disease Diagnosed at Elderly Age—an Increasing Distinct Entity? *Inflammatory Bowel Diseases*, 22(6), 1425-1434.
- Johns, M. W. 1991. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep*, 14(6), 540-545.

- Johns, M. W. 2000. Sensitivity and Specificity of the Multiple Sleep Latency Test (Mslt), the Maintenance of Wakefulness Test and the Epworth Sleepiness Scale: Failure of the Mslt as a Gold Standard. *Journal of Sleep Research*, 9(1), 5-11.
- Johnston, M. & Dixon, D. 2008. Current Issues and New Directions in Psychology and Health: What Happened to Behaviour in the Decade of Behaviour? *Psychol Health*, 23(5), 509-13.
- Jonefjäll, B., Simrén, M., Lasso, A., Öhman, L. & Strid, H. 2017. Psychological Distress, Iron Deficiency, Active Disease and Female Gender Are Independent Risk Factors for Fatigue in Patients with Ulcerative Colitis. *United European Gastroenterology Journal*, 6(1), 148-158.
- Jones, D., Gray, J. & Newton, J. 2009. Perceived Fatigue Is Comparable between Different Disease Groups. *QJM: An International Journal of Medicine*, 102(9), 617-624.
- Jonkman, N. H., Groenwold, R. H., Trappenburg, J. C., Hoes, A. W. & Schuurmans, M. J. 2017. Complex Self-Management Interventions in Chronic Disease Unravelling: A Review of Lessons Learned from an Individual Patient Data Meta-Analysis. *Journal of Clinical Epidemiology*, 83(1), 48-56.
- Jordan, C., Ohlsen, R., Hayee, B. H. & Chalder, T. 2017. A Qualitative Study Exploring the Experience of People with Ibd and Elevated Symptoms of Anxiety and Low Mood and the Type of Psychological Help They Would Like. *Psychology & Health*, 1(1), 1-18.
- Joseph, C., Sam, N., Maedhbh Etain, K. & Rona, M.-M. 2015. The Chalder Fatigue Questionnaire Is a Valid and Reliable Measure of Perceived Fatigue Severity in Multiple Sclerosis. *Multiple Sclerosis Journal*, 22(5), 677-684.
- Jostins, L., Ripke, S., Weersma, R. K., Duerr, R. H., McGovern, D. P., Hui, K. Y., Lee, J. C., Schumm, L. P., Sharma, Y. & Anderson, C. A. 2012. Host-Microbe Interactions Have Shaped the Genetic Architecture of Inflammatory Bowel Disease. *Nature*, 491(7422), 119-124.
- Ju, A., Unruh, M. L., Davison, S. N., Daputo, J., Dew, M. A., Fluck, R., Germain, M., Jassal, S. V., Obrador, G., O'donoghue, D., Tugwell, P., Craig, J. C., Ralph, A. F., Howell, M. & Tong, A. 2017. Patient-Reported Outcome Measures for Fatigue in Patients on Hemodialysis: A Systematic Review. *American Journal of Kidney Diseases*, 71(3), 327-343.
- Jump, R. L., Robinson, M. E., Armstrong, A. E., Barnes, E. V., Kilbourn, K. M. & Richards, H. B. 2005. Fatigue in Systemic Lupus Erythematosus: Contributions of Disease Activity, Pain, Depression, and Perceived Social Support. *Journal of Rheumatological Diseases*, 32(9), 1699-705.
- Kaambwa, B., Mpundu-Kaambwa, C., Adams, R., Appleton, S., Martin, S. & Wittert, G. 2016. Suitability of the Epworth Sleepiness Scale (Ess) for Economic Evaluation: An Assessment of Its Convergent and Discriminant Validity. *Behavioral Sleep Medicine*, 1(1), 1-26.
- Kant, I., Bültmann, U., Schröer, K., Beurskens, A., Van Amelsvoort, L. & Swaen, G. 2003. An Epidemiological Approach to Study Fatigue in the Working Population: The Maastricht Cohort Study. *Occupational and Environmental Medicine*, 60(S1), 32-39.
- Kappelman, M. D., Long, M. D., Martin, C., Dewalt, D. A., Kinner, P. M., Chen, W., Lewis, J. D. & Sandler, R. S. 2014. Evaluation of the Patient-Reported Outcomes Measurement Information System in a Large Cohort of Patients with Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology*, 12(8), 1315-1323.

- Kappelman, M. D., Rifas-Shiman, S. L., Porter, C. Q., Ollendorf, D. A., Sandler, R. S., Galanko, J. A. & Finkelstein, J. A. 2008. Direct Health Care Costs of Crohn's Disease and Ulcerative Colitis in Us Children and Adults. *Gastroenterology*, 135(6), 1907-1913.
- Karlsen, L. N., Carlsen, A., Omdal, R., Aabakken, L., Bolstad, N., Lundin, K. & Grimstad, T. 2017. P-125 Adalimumab Serum Concentrations or Anti-Drug Antibodies Do Not Influence Fatigue in Patients with Crohn's Disease. *Inflammatory Bowel Diseases*, 23(S44-S45).
- Karmiris, K., Paintaud, G., Noman, M., Magdelaine-Beuzelin, C., Ferrante, M., Degenne, D., Claes, K., Coopman, T., Van Schuerbeek, N. & Van Assche, G. 2009. Influence of Trough Serum Levels and Immunogenicity on Long-Term Outcome of Adalimumab Therapy in Crohn's Disease. *Gastroenterology*, 137(5), 1628-1640.
- Keeton, R. L., Mikocka-Walus, A. & Andrews, J. M. 2015. Concerns and Worries in People Living with Inflammatory Bowel Disease (Ibd): A Mixed Methods Study. *Journal of Psychosomatic Research*, 78(6), 573-578.
- Kendel, F., Wirtz, M., Dunkel, A., Lehmkuhl, E., Hetzer, R. & Regitz-Zagrosek, V. 2010. Screening for Depression: Rasch Analysis of the Dimensional Structure of the Phq-9 and the Hads-D. *Journal of Affective Disorders*, 122(3), 241-246.
- Khanna, R., Bressler, B., Levesque, B. G., Zou, G., Stitt, L. W., Greenberg, G. R., Panaccione, R., Bitton, A., Paré, P., Vermeire, S., D'haens, G., Macintosh, D., Sandborn, W. J., Donner, A., Vandervoort, M. K., Morris, J. C. & Feagan, B. G. 2015a. Early Combined Immunosuppression for the Management of Crohn's Disease (React): A Cluster Randomised Controlled Trial. *The Lancet*, 386(10006), 1825-1834.
- Khanna, R., Preiss, J. C., Macdonald, J. K. & Timmer, A. 2015b. Anti-Il-12/23p40 Antibodies for Induction of Remission in Crohn's Disease. *The Cochrane Database of Systematic Reviews*.
- Kirkevold, M., Bronken, B. A., Martinsen, R. & Kvigne, K. 2012. Promoting Psychosocial Well-Being Following a Stroke: Developing a Theoretically and Empirically Sound Complex Intervention. *International Journal of Nursing Studies*, 49(4), 386-397.
- Kitchenham, B. 2004. Procedures for Performing Systematic Reviews. *Keele, UK, Keele University*, 33(2004), 1-26.
- Kjærgaard, M., Arfwedson Wang, C. E., Waterloo, K. & Jorde, R. 2014. A Study of the Psychometric Properties of the Beck Depression Inventory-Ii, the Montgomery and Åsberg Depression Rating Scale, and the Hospital Anxiety and Depression Scale in a Sample from a Healthy Population. *Scandinavian Journal of Psychology*, 55(1), 83-89.
- Klevan, G., Jacobsen, C.O., Aarseth, J.H., Myhr, K.M., Nyland, H., Glad, S., Lode, K., Figved, N., Larsen, J.P. and Farbu, E., 2014. Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurologica Scandinavica*, 129(1), 21-26.
- Knoop, H., Bleijenberg, G., Gielissen, M. F., Van Der Meer, J. W. & White, P. D. 2007. Is a Full Recovery Possible after Cognitive Behavioural Therapy for Chronic Fatigue Syndrome? *Psychotherapy and Psychosomatics*, 76(3), 171-176.
- Knoop, H., Van Kessel, K. & Moss-Morris, R. 2012. Which Cognitions and Behaviours Mediate the Positive Effect of Cognitive Behavioural Therapy on Fatigue in Patients with Multiple Sclerosis? *Psychological Medicine*, 42(01), 205-213.

- Knowles, S., Wilson, J., Connell, W. & Kamm, M. 2011. Preliminary Examination of the Relations between Disease Activity, Illness Perceptions, Coping Strategies, and Psychological Morbidity in Crohn's Disease Guided by the Common Sense Model of Illness. *Inflammatory Bowel Diseases*, 17(12), 2551-2557.
- Knowles, S. R., Castle, D. J. & Monshat, K. 2013a. Efficacy and Methodological Challenges of Psychotherapy for Adults with Inflammatory Bowel Disease: A Review. *Inflammatory Bowel Diseases*, 19(12), 2704-2715.
- Knowles, S. R., Tribbick, D. & Cook, S. 2013b. Relationship between Health Status, Illness Perceptions, Coping Strategies and Psychological Morbidity: A Preliminary Study with Ibd Stoma Patients. *Journal of Crohn's and Colitis*, 7(10), e471-e478.
- Kok, G., Gottlieb, N. H., Peters, G.-J. Y., Mullen, P. D., Parcel, G. S., Ruiter, R. A., Fernández, M. E., Markham, C. & Bartholomew, L. K. 2016. A Taxonomy of Behaviour Change Methods: An Intervention Mapping Approach. *Health Psychology Review*, 10(3), 297-312.
- Kornbluth, A. & Sachar, D. B. 2010. Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. *The American Journal of Gastroenterology*, 105(3), 501-523.
- Kreijne, J. E., Lie, M. R. K. L., Vogelaar, L. & Van Der Woude, C. J. 2015. Practical Guideline for Fatigue Management in Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 10(1), 105-111.
- Kroenke, K., Spitzer, R. L. & Williams, J. B. 2001. The Phq-9: Validity of a Brief Depression Severity Measure. *Journal of General Internal Medicine*, 16(9), 606.
- Kroenke, K., Spitzer, R. L., Williams, J. B. & Lowe, B. 2010. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: A Systematic Review. *General Hospital Psychiatry*, 32(4), 345-59.
- Kwak, L., Kremers, S., Werkman, A., Visscher, T., Van Baak, M. & Brug, J. 2007. The Nhf-Nrg in Balance-Project: The Application of Intervention Mapping in the Development, Implementation and Evaluation of Weight Gain Prevention at the Worksite. *Obesity Reviews*, 8(4), 347-361.
- Kwakkenbos, L., Minton, O., Stone, P. C., Alexander, S., Baron, M., Hudson, M., Thombs, B. D., Baron, M., Hudson, M. & Khalidi, N. 2015. Can the Cancer-Related Fatigue Case-Definition Criteria Be Applied to Chronic Medical Illness? A Comparison between Breast Cancer and Systemic Sclerosis. *The Journal of rheumatology*, 42(7), 1156-1162.
- Kwasnicka, D., Dombrowski, S. U., White, M. & Sniehotta, F. 2016. Theoretical Explanations for Maintenance of Behaviour Change: A Systematic Review of Behaviour Theories. *Health Psychology Review*, 10(3), 277-296.
- Lamont, T., Barber, N., Pury, J. D., Fulop, N., Garfield-Birkbeck, S., Lilford, R., Mear, L., Raine, R. & Fitzpatrick, R. 2016. New Approaches to Evaluating Complex Health and Care Systems. *British Medical Journal*, 352(1), 152-154.
- Lancaster, G. A., Dodd, S. & Williamson, P. R. 2001. Design and Analysis of Pilot Studies: Recommendations for Good Practice. *Journal of Evaluation in Clinical Practice*, 10(2), 307-312.

- Langer, D. A., Mcleod, B. D. & Weisz, J. R. 2011. Do Treatment Manuals Undermine Youth–Therapist Alliance in Community Clinical Practice? *Journal of Consulting and Clinical Psychology*, 79(4), 427.
- Langhorst, J., Hofstetter, A., Wolfe, F. & Häuser, W. 2013. Short-Term Stress, but Not Mucosal Healing nor Depression Was Predictive for the Risk of Relapse in Patients with Ulcerative Colitis: A Prospective 12-Month Follow-up Study. *Inflammatory Bowel Diseases*, 19(11), 2380-2386.
- Lee, E. C., Whitehead, A. L., Jacques, R. M. & Julious, S. A. 2014. The Statistical Interpretation of Pilot Trials: Should Significance Thresholds Be Reconsidered? *BMC Medical Research Methodology*, 14(1), 41.
- Lees, C., Barrett, J., Parkes, M. & Satsangi, J. 2011. New Ibd Genetics: Common Pathways with Other Diseases. *Gut*, 60(12), 1739-1753.
- Lefebvre, C., Eisinga, A., McDonald, S. & Paul, N. 2008. Enhancing Access to Reports of Randomized Trials Published World-Wide—the Contribution of Embase Records to the Cochrane Central Register of Controlled Trials (Central) in the Cochrane Library. *Emerging Themes in Epidemiology*, 5(1), 13.
- Leon, A. C., Davis, L. L. & Kraemer, H. C. 2011. The Role and Interpretation of Pilot Studies in Clinical Research. *Journal of Psychiatric Research*, 45(5), 626-629.
- Lerdal, A. & Kottorp, A. 2011. Psychometric Properties of the Fatigue Severity Scale-Rasch Analyses of Individual Responses in a Norwegian Stroke Cohort. *International Journal of Nursing Studies*, 48(48), 1258-1265.
- Levati, S., Campbell, P., Frost, R., Dougall, N., Wells, M., Donaldson, C. & Hagen, S. 2016. Optimisation of Complex Health Interventions Prior to a Randomised Controlled Trial: A Scoping Review of Strategies Used. *Pilot and Feasibility Studies*, 2(1), 1-17.
- Leventhal, H., Brissette, I. & Leventhal, E. A. 2003. *The Self-Regulation of Health and Illness Behaviour*, New York, Routledge.
- Leventhal, H., Meyer, D. & Nerenz, D. 1980. The Common Sense Representation of Illness Danger. *Contributions to Medical Psychology*, 2(1), 7-30.
- Leventhal, H., Phillips, L. A. & Burns, E. 2016. The Common-Sense Model of Self-Regulation (Csm): A Dynamic Framework for Understanding Illness Self-Management. *Journal of Behavioral Medicine*, 39(6), 935-946.
- Levesque, B. G., Sandborn, W. J., Ruel, J., Feagan, B. G., Sands, B. E. & Colombel, J.-F. 2015. Converging Goals of Treatment of Inflammatory Bowel Disease from Clinical Trials and Practice. *Gastroenterology*, 148(1), 37-51.
- Levin, K. A. 2006. Study Design: Cross-Sectional Studies. *Evidence-Based Dentistry*, 7(1), 24-25.
- Lewin, S., Glenton, C. & Oxman, A. D. 2009. Use of Qualitative Methods Alongside Randomised Controlled Trials of Complex Healthcare Interventions: Methodological Study. *British Medical Journal*, 339(

- Lewis, C., Roberts, N., Vick, T. & Bisson, J. 2013. Development of a Guided Self-Help (Gsh) Program for the Treatment of Mild-to-Moderate Posttraumatic Stress Disorder (Ptsd). *Depression and Anxiety*, 30(11), 1121.
- Li, Y., Ren, J., Wang, G., Gu, G., Wu, X., Ren, H., Hong, Z., Hu, D., Wu, Q. & Li, G. 2015. Diagnostic Delay in Crohn's Disease Is Associated with Increased Rate of Abdominal Surgery: A Retrospective Study in Chinese Patients. *Digestive and Liver Disease*, 47(7), 544-548.
- Linardon, J. & Brennan, L. 2017. The Effects of Cognitive-Behavioral Therapy for Eating Disorders on Quality of Life: A Meta-Analysis. *International Journal of Eating Disorders*.
- Lippke, S. & Ziegelmann, J. P. 2008. Theory-Based Health Behavior Change: Developing, Testing, and Applying Theories for Evidence-Based Interventions. *Applied Psychology*, 57(4), 698-716.
- Locock, L. & Smith, L. 2011. Personal Benefit, or Benefiting Others? Deciding Whether to Take Part in Clinical Trials. *Clinical Trials*, 8(1), 85-93.
- Loftus, C. G., Loftus, E. V., Harmsen, W. S., Zinsmeister, A. R., Tremaine, W. J., Melton, L. J. & Sandborn, W. J. 2007. Update on the Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota, 1940–2000. *Inflammatory Bowel Diseases*, 13(3), 254-261.
- Loftus, E., Schoenfeld, P. & Sandborn, W. 2002. The Epidemiology and Natural History of Crohn's Disease in Population-Based Patient Cohorts from North America: A Systematic Review. *Alimentary Pharmacology & Therapeutics*, 16(1), 51-60.
- Loftus, E. V. 2004. Clinical Epidemiology of Inflammatory Bowel Disease: Incidence, Prevalence, and Environmental Influences. *Gastroenterology*, 126(6), 1504-1517.
- Logan, R. F. 1998. Inflammatory Bowel Disease Incidence: Up, Down or Unchanged? *Gut*, 42(3), 309-311.
- Löhönen, J., Isohanni, M., Nieminen, P. & Miettunen, J. 2010. Coverage of the Bibliographic Databases in Mental Health Research. *Nordic Journal of Psychiatry*, 64(3), 181-188.
- Lönnfors, S., Vermeire, S. & Avedano, L. 2014. Ibd and Health-Related Quality of Life—Discovering the True Impact. *Journal of Crohn's and Colitis*, 8(10), 1281-1286.
- Lopez-Vivancos, J., Casellas, F., Badia, X., Vilaseca, J. & Malagelada, J.-R. 1999. Validation of the Spanish Version of the Inflammatory Bowel Disease Questionnaire on Ulcerative Colitis and Crohn's Disease. *Digestion*, 60(3), 274-280.
- Lovell, K., Bower, P., Richards, D., Barkham, M., Sibbald, B. & Roberts, C. 2008. Developing Guided Self-Help for Depression Using the Medical Research Council Complex Interventions Framework: A Description of the Modelling Phase and Results of an Exploratory Randomised Controlled Trial. *BMC Psychiatry*, 8(1), 91-101.
- Löwe, B., Decker, O., Müller, S., Brähler, E., Schellberg, D., Herzog, W. & Herzberg, P. Y. 2008. Validation and Standardization of the Generalized Anxiety Disorder Screener (Gad-7) in the General Population. *Medical care*, 46(3), 266-274.

- Löwe, B., Kroenke, K., Herzog, W. & Gräfe, K. 2004a. Measuring Depression Outcome with a Brief Self-Report Instrument: Sensitivity to Change of the Patient Health Questionnaire (Phq-9). *Journal of Affective Disorders*, 81(1), 61-66.
- Löwe, B., Unützer, J., Callahan, C. M., Perkins, A. J. & Kroenke, K. 2004b. Monitoring Depression Treatment Outcomes with the Patient Health Questionnaire-9. *Medical care*, 42(12), 1194-1201.
- Lukas, M. 2010. Inflammatory Bowel Disease as a Risk Factor for Colorectal Cancer. *Digestive Diseases*, 28(4-5), 619-624.
- Maaser, C., Langholz, E., Gordon, H., Burisch, J., Ellul, P., Ramirez, V. H., Karakan, T., Katsanos, K. H., Krustins, E., Levine, A., Mantzaris, G. J., O'morain, C., Strid, H., Yuksel, E. S. & Annese, V. 2017. European Crohn's and Colitis Organisation Topical Review on Environmental Factors in Ibd. *Journal of Crohn's and Colitis*, 11(8), 905-920.
- Madsen, S. M., Mirza, M. R., Holm, S., Hilsted, K. L., Kampmann, K. & Riis, P. 2002. Attitudes Towards Clinical Research Amongst Participants and Nonparticipants. *Journal of Internal Medicine*, 251(2), 156-68.
- Mahid, S. S., Minor, K. S., Soto, R. E., Hornung, C. A. & Galandiuk, S. Smoking and Inflammatory Bowel Disease: A Meta-Analysis. Mayo Clinic Proceedings, 2006. Elsevier, 1462-1471.
- Maleki, I., Taghvaei, T., Barzin, M., Amin, K. & Khalilian, A. 2015. Validation of the Persian Version of the Inflammatory Bowel Disease Questionnaire (Ibdq) in Ulcerative Colitis Patients. *Caspian Journal of Internal Medicine*, 6(1), 20.
- Mann, C. J. 2003. Observational Research Methods. Research Design Ii: Cohort, Cross Sectional, and Case-Control Studies. *Emergency Medicine Journal*, 20(1), 54-60.
- Martin-Subero, M., Anderson, G., Kanchanatawan, B., Berk, M. & Maes, M. 2016. Comorbidity between Depression and Inflammatory Bowel Disease Explained by Immune-Inflammatory, Oxidative, and Nitrosative Stress; Tryptophan Catabolite; and Gut–Brain Pathways. *CNS Spectrums*, 21(02), 184-198.
- Masachs, M., Casellas, F. & Malagelada, J. 2007. Spanish Translation, Adaptation, and Validation of the 32-Item Questionnaire on Quality of Life for Inflammatory Bowel Disease (Ibdq-32). *Revista espanola de enfermedades digestivas: organo oficial de la Sociedad Espanola de Patologia Digestiva*, 99(9), 511-519.
- Massoud, M. R., Barry, D., Murphy, A., Albrecht, Y., Sax, S. & Parchman, M. 2016. How Do We Learn About Improving Health Care: A Call for a New Epistemological Paradigm. *International Journal for Quality in Health Care*, 28(3), 420-424.
- Matcham, F., Ali, S., Hotopf, M. & Chalder, T. 2015. Psychological Correlates of Fatigue in Rheumatoid Arthritis: A Systematic Review. *Clinical Psychology Review*, 39(1), 16-29.
- Matini, L. & Ogden, J. 2016. A Qualitative Study of Patients' Experience of Living with Inflammatory Bowel Disease: A Preliminary Focus on the Notion of Adaptation. *Journal of Health Psychology*, 21(11), 2493-2502.
- Mbuagbaw, L., Thabane, M., Vanniyasingam, T., Debono, V. B., Kosa, S., Zhang, S., Ye, C., Parpia, S., Dennis, B. B. & Thabane, L. 2014. Improvement in the Quality of Abstracts in Major Clinical

Journals since Consort Extension for Abstracts: A Systematic Review. *Contemporary Clinical Trials*, 38(2), 245-250.

Mcandrew, L. M., Martin, J. L., Friedlander, M. L., Shaffer, K., Breland, J. Y., Slotkin, S. & Leventhal, H. 2017. The Common Sense of Counseling Psychology: Introducing the Common-Sense Model of Self-Regulation. *Counselling Psychology Quarterly*, 1-16.

Mcandrew, L. M., Musumeci-Szabó, T. J., Mora, P. A., Vileikyte, L., Burns, E., Halm, E. A., Leventhal, E. A. & Leventhal, H. 2008. Using the Common Sense Model to Design Interventions for the Prevention and Management of Chronic Illness Threats: From Description to Process. *British Journal of Health Psychology*, 13(2), 195-204.

Mccombie, A. M., Mulder, R. T. & Gearry, R. B. 2013. Psychotherapy for Inflammatory Bowel Disease: A Review and Update. *Journal of Crohn's and Colitis*, 7(12), 935-949.

Mcdonald, A. M., Knight, R. C., Campbell, M. K., Entwistle, V. A., Grant, A. M., Cook, J. A., Elbourne, D. R., Francis, D., Garcia, J. & Roberts, I. 2006. What Influences Recruitment to Randomised Controlled Trials? A Review of Trials Funded by Two Uk Funding Agencies. *Trials*, 7(1), 1-9.

Mcdonald, J. W., Tsoulis, D. J., Macdonald, J. K. & Feagan, B. G. 2012. Methotrexate for Induction of Remission in Refractory Crohn's Disease. *The Cochrane Library*.

Mcdonald, S., Taylor, L. & Adams, C. 1999. Searching the Right Database. A Comparison of Four Databases for Psychiatry Journals. *Health Libraries Review*, 16(3), 151-156.

Mcnelly, A. S., Nathan, I., Monti, M., Grimble, G., Norton, C., Bredin, F., Czuber-Dochan, W., Berliner, S., Gay, M. & Darvell, M. 2016. A Randomised Controlled Pilot Study Investigating the Effect of Increasing Physical Activity and/or Omega-3 Supplementation on Fatigue in Patients with Inflammatory Bowel Disease. *Gastrointestinal Nursing*, 14(8), 39-50.

Mehta, F. 2016. Report: Economic Implications of Inflammatory Bowel Disease and Its Management. *The American Journal of Managed Care*, 22(S3), 51-60.

Mein, G., Johal, S., Grant, R. L., Seale, C., Ashcroft, R. & Tinker, A. 2012. Predictors of Two Forms of Attrition in a Longitudinal Health Study Involving Ageing Participants: An Analysis Based on the Whitehall II Study. *BMC Medical Research Methodology*, 12(1), 164.

Menees, S. B., Powell, C., Kurlander, J., Goel, A. & Chey, W. D. 2015. A Meta-Analysis of the Utility of C-Reactive Protein, Erythrocyte Sedimentation Rate, Fecal Calprotectin, and Fecal Lactoferrin to Exclude Inflammatory Bowel Disease in Adults with Ibs. *The American Journal of Gastroenterology*, 110(3), 444-454.

Meucci, G., Bortoli, A., Riccioli, F. A., Girelli, C. M., Radaelli, F., Rivolta, R. & Tatarella, M. 1999. Frequency and Clinical Evolution of Indeterminate Colitis: A Retrospective Multi-Centre Study in Northern Italy. Gsmii (Gruppo Di Studio Per Le Malattie Infiammatorie Intestinali). *European Journal of Gastroenterology & Hepatology*, 11(8), 909-913.

Mezirow, J. 1998. On Critical Reflection. *Adult Education Quarterly*, 48(3), 185-198.

Michie, S. & Abraham, C. 2004. Interventions to Change Health Behaviours: Evidence-Based or Evidence-Inspired? *Psychology & Health*, 19(1), 29-49.

- Michie, S. & Abraham, C. 2008. Advancing the Science of Behaviour Change: A Plea for Scientific Reporting. *Addiction*, 103(9), 1409-1410.
- Michie, S., Abraham, C., Whittington, C., McAteer, J. & Gupta, S. 2009. Effective Techniques in Healthy Eating and Physical Activity Interventions: A Meta-Regression. *Health Psychology*, 28(6), 690-701.
- Michie, S., Johnston, M., Abraham, C., Lawton, R., Parker, D. & Walker, A. 2005. Making Psychological Theory Useful for Implementing Evidence Based Practice: A Consensus Approach. *Quality and safety in health care*, 14(1), 26-33.
- Michie, S., Johnston, M., Francis, J., Hardeman, W. & Eccles, M. 2008. From Theory to Intervention: Mapping Theoretically Derived Behavioural Determinants to Behaviour Change Techniques. *Applied Psychology*, 57(4), 660-680.
- Michie, S. & Prestwich, A. 2010. Are Interventions Theory-Based? Development of a Theory Coding Scheme. *Health Psychology*, 29(1), 1.
- Michie, S., Van Stralen, M. M. & West, R. 2011. The Behaviour Change Wheel: A New Method for Characterising and Designing Behaviour Change Interventions. *Implementation Science*, 6(1), 42.
- Mikocka-Walus, A., Andrews, J. M., Rampton, D., Goodhand, J., Van Der Woude, J. & Bernstein, C. N. 2014. How Can We Improve Models of Care in Inflammatory Bowel Disease? An International Survey of Ibd Health Professionals. *Journal of Crohn's and Colitis*, 8(12), 1668-1674.
- Mikocka-Walus, A., Bampton, P., Hetzel, D., Hughes, P., Esterman, A. & Andrews, J. M. 2015. Cognitive-Behavioural Therapy Has No Effect on Disease Activity but Improves Quality of Life in Subgroups of Patients with Inflammatory Bowel Disease: A Pilot Randomised Controlled Trial. *BMC Gastroenterology*, 15(1), 54.
- Mikocka-Walus, A., Bampton, P., Hetzel, D., Hughes, P., Esterman, A. & Andrews, J. M. 2017. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. *International Journal of Behavioral Medicine*, 24(1), 127-135.
- Mikocka-Walus, A., Knowles, S. R., Keefer, L. & Graff, L. 2016. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflammatory Bowel Diseases*, 22(3), 752-762.
- Mikocka-Walus, A., Turnbull, D., Andrews, J. M., Moulding, N., Wilson, I. & Holtmann, G. 2009. Psychogastroenterology: A Call for Psychological Input in Australian Gastroenterology Clinics. *Internal Medicine Journal*, 39(2), 127-130.
- Milette, K., Hudson, M., Baron, M. & Thombs, B. D. 2010. Comparison of the Phq-9 and Ces-D Depression Scales in Systemic Sclerosis: Internal Consistency Reliability, Convergent Validity and Clinical Correlates. *Rheumatology*, 49(4), 789-796.
- Miligkos, M., Papamichael, K., Castele, N. V., Mantzaris, G. J., Gils, A., Levesque, B. G. & Zintzaras, E. 2016. Efficacy and Safety Profile of Anti-Tumor Necrosis Factor-A Versus Anti-Integrin Agents for the Treatment of Crohn's Disease: A Network Meta-Analysis of Indirect Comparisons. *Clinical therapeutics*, 38(6), 1342-1358. e6.
- Miller, W. R. & Rollnick, S. 2014. The Effectiveness and Ineffectiveness of Complex Behavioral Interventions: Impact of Treatment Fidelity. *Contemporary Clinical Trials*, 37(2), 234-241.

- Minderhoud, I. M., Samsom, M. & Oldenburg, B. 2007. Crohn's Disease, Fatigue, and Infliximab: Is There a Role for Cytokines in the Pathogenesis of Fatigue? *World Journal of Gastroenterology*, 13(14), 2089-2093.
- Moher, D., Glasziou, P., Chalmers, I., Nasser, M., Bossuyt, P. M., Korevaar, D. A., Graham, I. D., Ravaud, P. & Boutron, I. 2016. Increasing Value and Reducing Waste in Biomedical Research: Who's Listening? *The Lancet*, 387(10027), 1573-1586.
- Moher, D., Schulz, K. F. & Altman, D. G. 2001. The Consort Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomised Trials. *The Lancet*, 357(9263), 1191-1194.
- Moher, D., Simera, I., Schulz, K., Miller, D., Grimshaw, J., Hoey, J. & Altman, D. Reporting Guidelines for Clinical Research: A Systematic Review. 6th International Congress on Peer Review and Biomedical Publication, Vancouver, 2009.
- Moher, D., Simera, I., Schulz, K. F., Hoey, J. & Altman, D. G. 2008. Helping Editors, Peer Reviewers and Authors Improve the Clarity, Completeness and Transparency of Reporting Health Research. *BMC Medicine*, 6(1), 13.
- Moher, D. & Tsertsvadze, A. 2006. Systematic Reviews: When Is an Update an Update? *The Lancet*, 367(9514), 881-883.
- Mohr, D. C., Hart, S. L., Julian, L., Catledge, C., Honos-Webb, L., Vella, L. & Tasch, E. T. 2005. Telephone-Administered Psychotherapy for Depression. *Archives of General Psychiatry*, 62(9), 1007-14.
- Mohr, D. C., Ho, J., Duffecy, J., Reifler, D., Sokol, L., Burns, M. N., Jin, L. & Siddique, J. 2012. Effect of Telephone-Administered Vs Face-to-Face Cognitive Behavioral Therapy on Adherence to Therapy and Depression Outcomes among Primary Care Patients: A Randomized Trial. *Journal of the American Medical Association*, 307(21), 2278-85.
- Mohr, D. C., Siddique, J., Ho, J., Duffecy, J., Jin, L. & Fokuo, J. K. 2010. Interest in Behavioral and Psychological Treatments Delivered Face-to-Face, by Telephone, and by Internet. *Annals of Behavioral Medicine*, 40(1), 89-98.
- Mohr, D. C., Vella, L., Hart, S., Heckman, T. & Simon, G. 2008. The Effect of Telephone-Administered Psychotherapy on Symptoms of Depression and Attrition: A Meta-Analysis. *Clinical Psychology: Science and Practice*, 15(3), 243-253.
- Molander, P., Färkkilä, M., Ristimäki, A., Salminen, K., Kemppainen, H., Blomster, T., Koskela, R., Jussila, A., Rautiainen, H. & Nissinen, M. 2015. Does Fecal Calprotectin Predict Short-Term Relapse after Stopping Tnf α -Blocking Agents in Inflammatory Bowel Disease Patients in Deep Remission? *Journal of Crohn's and Colitis*, 9(1), 33-40.
- Molodecky, N. A., Soon, S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., Benchimol, E. I., Panaccione, R., Ghosh, S. & Barkema, H. W. 2012. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases with Time, Based on Systematic Review. *Gastroenterology*, 142(1), 46-54.
- Moore, C. G., Carter, R. E., Nietert, P. J. & Stewart, P. W. 2011. Recommendations for Planning Pilot Studies in Clinical and Translational Research. *Clinical and Translational Science*, 4(5), 332-337.

- Moore, G. F., Audrey, S., Barker, M., Bond, L., Bonell, C., Hardeman, W., Moore, L., O'cathain, A., Tinati, T., Wight, D. & Baird, J. 2015. Process Evaluation of Complex Interventions: Medical Research Council Guidance. *British Medical Journal*, 350(1), 1-15.
- Moore, G. F. & Evans, R. E. 2017. What Theory, for Whom and in Which Context? Reflections on the Application of Theory in the Development and Evaluation of Complex Population Health Interventions. *SSM - Population Health*, 3(1), 132-135.
- Morrison, A., Polisena, J., Husereau, D., Moulton, K., Clark, M., Fiander, M., Mierzwinski-Urban, M., Clifford, T., Hutton, B. & Rabb, D. 2012. The Effect of English-Language Restriction on Systematic Review-Based Meta-Analyses: A Systematic Review of Empirical Studies. *International Journal of Technology Assessment in Health Care*, 28(02), 138-144.
- Moss-Morris, R., Mcalpine, L., Didsbury, L. & Spence, M. 2010. A Randomized Controlled Trial of a Cognitive Behavioural Therapy-Based Self-Management Intervention for Irritable Bowel Syndrome in Primary Care. *Psychological Medicine*, 40(1), 85-94.
- Moss-Morris, R., Mccrone, P., Yardley, L., Van Kessel, K., Wills, G. & Dennison, L. 2012. A Pilot Randomised Controlled Trial of an Internet-Based Cognitive Behavioural Therapy Self-Management Programme (Ms Invigor8) for Multiple Sclerosis Fatigue. *Behaviour Research and Therapy*, 50(6), 415-421.
- Mowat, C., Cole, A., Windsor, A., Ahmad, T., Arnott, I., Driscoll, R., Mitton, S., Orchard, T., Rutter, M. & Younge, L. 2011. Guidelines for the Management of Inflammatory Bowel Disease in Adults. *Gut*, 60(5), 571-607.
- Muller, I. & Yardley, L. 2011. Telephone-Delivered Cognitive Behavioural Therapy: A Systematic Review and Meta-Analysis. *Journal of Telemedicine and Telecare*, 17(4), 177-184.
- Mulligan, J., Haddock, G., Hartley, S., Davies, J., Sharp, T., Kelly, J., Neil, S. T., Taylor, C. D., Welford, M. & Price, J. 2014. An Exploration of the Therapeutic Alliance within a Telephone-Based Cognitive Behaviour Therapy for Individuals with Experience of Psychosis. *Psychology and Psychotherapy: Theory, Research and Practice*, 87(4), 393-410.
- Multone, E., Vader, J.-P., Mottet, C., Schoepfer, A., Fournier, N., Burnand, B., Michetti, P. & Pittet, V. 2015. Characteristics of Non-Responders to Self-Reported Questionnaires in a Large Inflammatory Bowel Disease Cohort Study. *Scandinavian Journal of Gastroenterology*, 50(11), 1348-1356.
- Murchie, P., Hannaford, P. C., Wyke, S., Nicolson, M. C. & Campbell, N. C. 2007. Designing an Integrated Follow-up Programme for People Treated for Cutaneous Malignant Melanoma: A Practical Application of the Mrc Framework for the Design and Evaluation of Complex Interventions to Improve Health. *Family Practice*, 24(3), 283-292.
- Nelson, G., Macnaughton, E. & Goering, P. 2015. What Qualitative Research Can Contribute to a Randomized Controlled Trial of a Complex Community Intervention. *Contemporary Clinical Trials*, 45(B), 377-384.
- Neta, G., Glasgow, R. E., Carpenter, C. R., Grimshaw, J. M., Rabin, B. A., Fernandez, M. E. & Brownson, R. C. 2015. A Framework for Enhancing the Value of Research for Dissemination and Implementation. *American Journal of Public Health*, 105(1), 49-57.

- Neuendorf, R., Harding, A., Stello, N., Hanes, D. & Wahbeh, H. 2016. Depression and Anxiety in Patients with Inflammatory Bowel Disease: A Systematic Review. *Journal of Psychosomatic Research*, 87(1), 70-80.
- Newby, J. M., Mckinnon, A., Kuyken, W., Gilbody, S. & Dalglish, T. 2015. Systematic Review and Meta-Analysis of Transdiagnostic Psychological Treatments for Anxiety and Depressive Disorders in Adulthood. *Clinical Psychology Review*, 40(1), 91-110.
- Newington, L. & Metcalfe, A. 2014. Factors Influencing Recruitment to Research: Qualitative Study of the Experiences and Perceptions of Research Teams. *BMC Medical Research Methodology*, 14(1), 10.
- Ng, S. C., Shi, H. Y., Hamidi, N., Underwood, F. E., Tang, W., Benchimol, E. I., Panaccione, R., Ghosh, S., Wu, J. C. Y., Chan, F. K. L., Sung, J. J. Y. & Kaplan, G. G. 2017. Worldwide Incidence and Prevalence of Inflammatory Bowel Disease in the 21st Century: A Systematic Review of Population-Based Studies. *The Lancet*, 390(10114), 2769-2778.
- Ng, S. C., Tang, W., Leong, R. W., Chen, M., Ko, Y., Studd, C., Niewiadomski, O., Bell, S., Kamm, M. A. & De Silva, H. 2014. Environmental Risk Factors in Inflammatory Bowel Disease: A Population-Based Case-Control Study in Asia-Pacific. *Gut*, 64(7), 2014-307410.
- Nicholas, D. B., Otley, A., Smith, C., Avolio, J., Munk, M. & Griffiths, A. M. 2007. Challenges and Strategies of Children and Adolescents with Inflammatory Bowel Disease: A Qualitative Examination. *Health and Quality of Life Outcomes*, 5(1), 28.
- Noar, S. M. & Zimmerman, R. S. 2005. Health Behavior Theory and Cumulative Knowledge Regarding Health Behaviors: Are We Moving in the Right Direction? *Health Education Research*, 20(3), 275-290.
- Norton, C., Czuber-Dochan, W., Bassett, P., Berliner, S., Bredin, F., Darvell, M., Forbes, A., Gay, M., Ream, E. & Terry, H. 2015. Assessing Fatigue in Inflammatory Bowel Disease: Comparison of Three Fatigue Scales. *Alimentary Pharmacology & Therapeutics*, 42(2), 203-211.
- Norton, S., Cosco, T., Doyle, F., Done, J. & Sacker, A. 2013. The Hospital Anxiety and Depression Scale: A Meta Confirmatory Factor Analysis. *Journal of Psychosomatic Research*, 74(1), 74-81.
- Noyes, J., Gough, D., Lewin, S., Mayhew, A., Michie, S., Pantoja, T., Petticrew, M., Pottie, K., Rehfuss, E. & Shemilt, I. 2013. A Research and Development Agenda for Systematic Reviews That Ask Complex Questions About Complex Interventions. *Journal of Clinical Epidemiology*, 66(11), 1262-1270.
- O'brien, N., Heaven, B., Teal, G., Evans, E. H., Cleland, C., Moffatt, S., Sniehotta, F. F., White, M., Mathers, J. C. & Moynihan, P. 2016. Integrating Evidence from Systematic Reviews, Qualitative Research, and Expert Knowledge Using Co-Design Techniques to Develop a Web-Based Intervention for People in the Retirement Transition. *Journal of Medical Internet Research*, 18(8), e210.
- O'connor, M., Bager, P., Duncan, J., Gaarenstroom, J., Younge, L., Détré, P., Bredin, F., Dibley, L., Dignass, A. & Barrero, M. G. 2013. N-Ecco Consensus Statements on the European Nursing Roles in Caring for Patients with Crohn's Disease or Ulcerative Colitis. *Journal of Crohn's and Colitis*, 7(9), 744-764.

- O'cathain, A., Goode, J., Drabble, S. J., Thomas, K. J., Rudolph, A. & Hewison, J. 2014. Getting Added Value from Using Qualitative Research with Randomized Controlled Trials: A Qualitative Interview Study. *Trials*, 15(
- O'cathain, A., Hoddinott, P., Lewin, S., Thomas, K. J., Young, B., Adamson, J., Jansen, Y. J., Mills, N., Moore, G. & Donovan, J. L. 2015. Maximising the Impact of Qualitative Research in Feasibility Studies for Randomised Controlled Trials: Guidance for Researchers. *Pilot and Feasibility Studies*, 15(1), 215-230.
- Ofcom. 2017. *Communications Market Report 2017, United Kingdom* [Online]. Available: https://www.ofcom.org.uk/data/assets/pdf_file/0017/105074/cmr-2017-uk.pdf [Accessed 11 October 2017].
- Olaithe, M., Skinner, T. C., Clarke, J., Eastwood, P. & Bucks, R. S. 2013. Can We Get More from the Epworth Sleepiness Scale (Ess) Than Just a Single Score? *Sleep and Breathing*, 17(2), 763-769.
- Paasche-Orlow, M. K., Taylor, H. A. & Brancati, F. L. 2003. Readability Standards for Informed-Consent Forms as Compared with Actual Readability. *New England Journal of Medicine* 348(8), 721-6.
- Painter, J. E., Borba, C. P., Hynes, M., Mays, D. & Glanz, K. 2008. The Use of Theory in Health Behavior Research from 2000 to 2005: A Systematic Review. *Annals of Behavioral Medicine*, 35(3), 358.
- Palmer, J., Bozas, G., Stephens, A., Johnson, M., Avery, G. & O Toole, L. 2013. Developing a Complex Intervention for the Outpatient Management of Incidentally Diagnosed Pulmonary Embolism in Cancer Patients. *BMC Health Services Research*, 13(1), 235-245.
- Panara, A., Yarur, A., Rieders, B., Proksell, S., Deshpande, A. R., Abreu, M. T. & Sussman, D. A. 2014. The Incidence and Risk Factors for Developing Depression after Being Diagnosed with Inflammatory Bowel Disease: A Cohort Study. *Alimentary Pharmacology & Therapeutics*, 39(8), 802-810.
- Panes, J., Bouhnik, Y., Reinisch, W., Stoker, J., Taylor, S., Baumgart, D., Danese, S., Halligan, S., Marincek, B. & Matos, C. 2013. Imaging Techniques for Assessment of Inflammatory Bowel Disease: Joint Ecco and Esgar Evidence-Based Consensus Guidelines. *Journal of Crohn's and Colitis*, 7(7), 556-585.
- Papaioannou, D., Sutton, A., Carroll, C., Booth, A. & Wong, R. 2010. Literature Searching for Social Science Systematic Reviews: Consideration of a Range of Search Techniques. *Health Information & Libraries Journal*, 27(2), 114-122.
- Park, K., Colletti, R. B., Rubin, D. T., Sharma, B. K., Thompson, A. & Krueger, A. 2016. Health Insurance Paid Costs and Drivers of Costs for Patients with Crohn's Disease in the United States. *The American Journal of Gastroenterology*, 111(1), 15-23.
- Parkes, G. C., Whelan, K. & Lindsay, J. O. 2014. Smoking in Inflammatory Bowel Disease: Impact on Disease Course and Insights into the Aetiology of Its Effect. *Journal of Crohn's and Colitis*, 8(8), 717-725.
- Patejdl, R., Penner, I. K., Noack, T. K. & Zettl, U. K. 2016. Multiple Sclerosis and Fatigue: A Review on the Contribution of Inflammation and Immune-Mediated Neurodegeneration. *Autoimmunity Reviews*, 15(3), 210-220.

- Patel, V., Wang, Y., Macdonald, J. K., McDonald, J. W. & Chande, N. 2014. Methotrexate for Maintenance of Remission in Crohn's Disease. *The Cochrane Library*.
- Payne, J. K. & Hendrix, C. C. 2010. Clinical Trial Recruitment Challenges with Older Adults with Cancer. *Applied Nursing Research*, 23(4), 233-237.
- Perepletchikova, F., Treat, T. A. & Kazdin, A. E. 2007. Treatment Integrity in Psychotherapy Research: Analysis of the Studies and Examination of the Associated Factors. *Journal of Consulting and Clinical Psychology*, 75(6), 829-841.
- Peters, M. D., Godfrey, C. M., Khalil, H., Mcinerney, P., Parker, D. & Soares, C. B. 2015. Guidance for Conducting Systematic Scoping Reviews. *International Journal of Evidence-Based Healthcare*, 13(3), 141-146.
- Peyrin-Biroulet, L., Colombel, J.-F., Feagan, B. G., Panés, J., Sandborn, W. J., Vermeire, S., Danese, S., Hanauer, S. B. & Rycroft, B. 2016a. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. *Clinical Gastroenterology and Hepatology*, 14(3), 348-354. e17.
- Peyrin-Biroulet, L., Colombel, J.-F. & Ghosh, S. 2016b. Preventing Collateral Damage in the Inflammatory Bowel Disease Patient: Using Disease Assessment and Prognostic Factors to Optimise Clinical Outcomes *European Medical Journal Reviews*, 5(1), 28-33.
- Peyrin-Biroulet, L., Fiorino, G., Buisson, A. & Danese, S. 2013. First-Line Therapy in Adult Crohn's Disease: Who Should Receive Anti-Tnf Agents? *Nature Reviews Gastroenterology and Hepatology*, 10(6), 345-351.
- Peyrin-Biroulet, L., Sandborn, W., Sands, B. E., Reinisch, W., Bemelman, W., Bryant, R. V., D'haens, G., Dotan, I., Dubinsky, M., Feagan, B., Fiorino, G., Geary, R., Krishnareddy, S., Lakatos, P. L., Loftus Jr, E. V., Marteau, P., Munkholm, P., Murdoch, T. B., Ordas, I., Panaccione, R., Riddell, R. H., Ruel, J., Rubin, D. T., Samaan, M., Siegel, C. A., Silverberg, M. S., Stoker, J., Schreiber, S., Travis, S., Van Assche, G., Danese, S., Panes, J., Bouguen, G., O'donnell, S., Pariente, B., Winer, S., Hanauer, S. & Colombel, J. F. 2015. Selecting Therapeutic Targets in Inflammatory Bowel Disease (Stride): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol*, 110(9), 1324-1338.
- Pfadenhauer, L. M., Gerhardus, A., Mozygemba, K., Lysdahl, K. B., Booth, A., Hofmann, B., Wahlster, P., Polus, S., Burns, J. & Brereton, L. 2017. Making Sense of Complexity in Context and Implementation: The Context and Implementation of Complex Interventions Framework. *Implementation Science*, 12(1), 21-32.
- Picariello, F., Moss-Morris, R., Macdougall, I. C., Norton, S., Da Silva-Gane, M., Farrington, K., Clayton, H. & Chilcot, J. 2018. Cognitive-Behavioural Therapy (Cbt) for Renal Fatigue (Bref): A Feasibility Randomised-Controlled Trial of Cbt for the Management of Fatigue in Haemodialysis (Hd) Patients. *British Medical Journal Open*, 8(3).
- Pittet, V., Vaucher, C., Froehlich, F., Burnand, B., Michetti, P., Maillard, M. H. & Group, S. I. C. S. 2017. Patient Self-Reported Concerns in Inflammatory Bowel Diseases: A Gender-Specific Subjective Quality-of-Life Indicator. *PLOS One*, 12(2), 1-16.
- Pittson, H. & Wallace, L. 2011. Using Intervention Mapping to Develop a Family-Based Childhood Weight Management Programme. *Journal of Health Services Research & Policy*, 16(S1), 2-7.

- Plain English Campaign. 2017. *How to Write in Plain English* [Online]. Available: <http://www.plainenglish.co.uk/files/howto.pdf>.
- Plummer, F., Manea, L., Trepel, D. & Mcmillan, D. 2016. Screening for Anxiety Disorders with the Gad-7 and Gad-2: A Systematic Review and Diagnostic Metaanalysis. *General Hospital Psychiatry*, 39(1), 24-31.
- Ponder, A. & Long, M. D. 2013. A Clinical Review of Recent Findings in the Epidemiology of Inflammatory Bowel Disease. *Clinical Epidemiology*, 5(237).
- Popp, R. F., Fierlbeck, A. K., Knüttel, H., König, N., Rupprecht, R., Weissert, R. & Wetter, T. C. 2017. Daytime Sleepiness Versus Fatigue in Patients with Multiple Sclerosis: A Systematic Review on the Epworth Sleepiness Scale as an Assessment Tool. *Sleep Medicine Reviews*, 32(95-108).
- Prestwich, A., Sniehotta, F., Whittington, C., Dombrowski, S., Rogers, L. & Michie, S. 2014. Does Theory Influence the Effectiveness of Health Behavior Interventions? Meta-Analysis. *Health Psychology*, 33(5), 465-474.
- Prestwich, A., Webb, T. L. & Conner, M. 2015. Using Theory to Develop and Test Interventions to Promote Changes in Health Behaviour: Evidence, Issues, and Recommendations. *Current Opinion in Psychology*, 5(1), 1-5.
- Price, J. H. & Murnan, J. 2004. *Research Limitations and the Necessity of Reporting Them*. Taylor & Francis.
- Protheroe, J., Whittle, R., Bartlam, B., Estacio, E. V., Clark, L. & Kurth, J. 2017. Health Literacy, Associated Lifestyle and Demographic Factors in Adult Population of an English City: A Cross-Sectional Survey. *Health Expectations*, 20(1), 112-119.
- Protogerou, C. & Johnson, B. T. 2014. Factors Underlying the Success of Behavioral Hiv-Prevention Interventions for Adolescents: A Meta-Review. *AIDS and Behavior*, 18(10), 1847-1863.
- Ratnakumaran, R., Warren, L., Gracie, D. J., Sagar, R. C., Hamlin, P. J., O'connor, A. & Ford, A. C. 2017. Fatigue in Inflammatory Bowel Disease Reflects Mood And symptom-Reporting Behavior Rather Than Biochemical Activity or Anemia. *Clinical Gastroenterology and Hepatology*, 1(In press), 1-3.
- Redfern, J., Mckevitt, C. & Wolfe, C. D. 2006. Development of Complex Interventions in Stroke Care. *Stroke*, 37(9), 2410-2419.
- Redfern, J., Rudd, A. D., Wolfe, C. D. & Mckevitt, C. 2008. Stop Stroke: Development of an Innovative Intervention to Improve Risk Factor Management after Stroke. *Patient Education and Counseling*, 72(2), 201-209.
- Reelick, M. F. 2011. *One Step at a Time: Disentangling the Complexity of Preventing Falls in Frail Older Persons*. Radboud University Nijmegen.
- Regueiro, M. D., Greer, J. B. & Hanauer, S. B. 2016. Established Management Paradigms in Ibd: Treatment Targets and Therapeutic Tools. *The American Journal of Gastroenterology Supplements*, 3(3), 8-16.

- Rehfuess, E. A., Booth, A., Brereton, L., Burns, J., Gerhardus, A., Mozygemba, K., Oortwijn, W., Pfadenhauer, L. M., Tummers, M. & Wilt, V. D. G. 2017. Towards a Taxonomy of Logic Models in Systematic Reviews and Health Technology Assessments: A Priori, Staged, and Iterative Approaches. *Research Synthesis Methods*, 1(1), 1-15.
- Reinisch, W., Sandborn, W. J., Rutgeerts, P., Feagan, B. G., Rachmilewitz, D., Hanauer, S. B., Lichtenstein, G. R., De Villiers, W. J., Blank, M. & Lang, Y. 2012. Long-Term Infliximab Maintenance Therapy for Ulcerative Colitis: The Act-1 and-2 Extension Studies. *Inflammatory bowel diseases*, 18(2), 201-211.
- Ren, W. H., Lai, M., Chen, Y., Irvine, E. J. & Zhou, Y. 2007. Validation of the Mainland Chinese Version of the Inflammatory Bowel Disease Questionnaire (Ibdq) for Ulcerative Colitis and Crohn's Disease. *Inflammatory Bowel Diseases*, 13(7), 903-910.
- Riley, B. L., Macdonald, J., Mansi, O., Kothari, A., Kurtz, D. & Edwards, N. C. 2008. Is Reporting on Interventions a Weak Link in Understanding How and Why They Work? A Preliminary Exploration Using Community Heart Health Exemplars. *Implementation Science*, 3(1), 27.
- Rivière, P., Zallot, C., Desobry, P., Sabaté, J., Vergniol, J., Zerbib, F., Peyrin-Biroulet, L., Laharie, D. & Poullenot, F. 2017. Frequency of and Factors Associated with Sexual Dysfunction in Patients with Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, 11(11), 1347-1352.
- Robinson, L., Francis, J., James, P., Tindle, N., Greenwell, K. & Rodgers, H. 2005. Caring for Carers of People with Stroke: Developing a Complex Intervention Following the Medical Research Council Framework. *Clinical Rehabilitation*, 19(5), 560-571.
- Rochelle, T. L. & Fidler, H. 2013. The Importance of Illness Perceptions, Quality of Life and Psychological Status in Patients with Ulcerative Colitis and Crohn's Disease. *Journal of Health Psychology*, 18(7), 972-983.
- Rogler, G. 2013. Top-Down or Step-up Treatment in Crohn's Disease? *Digestive Diseases*, 31(1), 83-90.
- Rohwer, A., Pfadenhauer, L., Burns, J., Brereton, L., Gerhardus, A., Booth, A., Oortwijn, W. & Rehfuess, E. 2017. Logic Models Help Make Sense of Complexity in Systematic Reviews and Health Technology Assessments. *Journal of Clinical Epidemiology*, 83(37-47).
- Roth, A. & Fonagy, P. 2013. *What Works for Whom?: A Critical Review of Psychotherapy Research*, Guilford Publications.
- Rothman, A. J. 2004. "Is There Nothing More Practical Than a Good Theory?": Why Innovations and Advances in Health Behavior Change Will Arise If Interventions Are Used to Test and Refine Theory. *The International Journal of Behavioral Nutrition and Physical Activity*, 1(1), 1-7.
- Rowlands, G., Protheroe, J., Winkley, J., Richardson, M., Seed, P. T. & Rudd, R. 2015. A Mismatch between Population Health Literacy and the Complexity of Health Information: An Observational Study. *British Journal of General Practice*, 65(635), e379-86.
- Rowlands, G., Sims, J. & Kerry, S. 2005. A Lesson Learnt: The Importance of Modelling in Randomized Controlled Trials for Complex Interventions in Primary Care. *Family Practice*, 22(1), 132-139.
- Royle, P., Bain, L. & Waugh, N. 2005. Systematic Reviews of Epidemiology in Diabetes: Finding the Evidence. *BMC Medical Research Methodology*, 5(1), 2-20.

- Rubin, G., Hungin, A., Kelly, P. & Ling, J. 2000. Inflammatory Bowel Disease: Epidemiology and Management in an English General Practice Population. *Alimentary Pharmacology & Therapeutics*, 14(12), 1553-1559.
- Ruiz, M. A., Zamorano, E., García-Campayo, J., Pardo, A., Freire, O. & Rejas, J. 2011. Validity of the Gad-7 Scale as an Outcome Measure of Disability in Patients with Generalized Anxiety Disorders in Primary Care. *Journal of Affective Disorders*, 128(3), 277-286.
- Rutgeerts, P. 2012. How to Guide Therapeutic Decisions in a Patient-Tailored Approach to Treatment of Ibd? *Digestive Diseases*, 30(4), 396-399.
- Rychetnik, L., Frommer, M., Hawe, P. & Shiell, A. 2002. Criteria for Evaluating Evidence on Public Health Interventions. *Journal of Epidemiology & Community Health*, 56(2), 119-127.
- Sackett, D. L., Rosenberg, W. M., Gray, J. M., Haynes, R. B. & Richardson, W. S. 1996. *Evidence Based Medicine: What It Is and What It Isn't*, British Medical Journal Publishing Group.
- Salmoiraghi, A. & Sambhi, R. 2010. Early Termination of Cognitive-Behavioural Interventions: Literature Review. *The Psychiatrist*, 34(12), 529-532.
- Samaan, Z., Mbuagbaw, L., Kosa, D., Borg Debono, V., Dillenburg, R., Zhang, S., Fruci, V., Dennis, B., Bawor, M. & Thabane, L. 2013. A Systematic Scoping Review of Adherence to Reporting Guidelines in Health Care Literature. *Journal of Multidisciplinary Healthcare*, 6(1), 169-188.
- Sandborn, W. & Hanauer, S. 2003. The Pharmacokinetic Profiles of Oral Mesalazine Formulations and Mesalazine Pro-Drugs Used in the Management of Ulcerative Colitis. *Alimentary Pharmacology & Therapeutics*, 17(1), 29-42.
- Sandborn, W. J., Feagan, B. G., Rutgeerts, P., Hanauer, S., Colombel, J.-F., Sands, B. E., Lukas, M., Fedorak, R. N., Lee, S. & Bressler, B. 2013. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. *New England Journal of Medicine*, 369(8), 711-721.
- Sands, B. E. 2015. Biomarkers of Inflammation in Inflammatory Bowel Disease. *Gastroenterology*, 149(5), 1275-1285.
- Sands, B. E., Feagan, B. G., Rutgeerts, P., Colombel, J.-F., Sandborn, W. J., Sy, R., D'haens, G., Ben-Horin, S., Xu, J. & Rosario, M. 2014. Effects of Vedolizumab Induction Therapy for Patients with Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed. *Gastroenterology*, 147(3), 618-627. e3.
- Sarkar, S. & Gupta, R. 2012. Telephone Vs Face-to-Face Cognitive Behavioral Therapy for Depression. *Journal of the American Medical Association*, 308(11), 1090-1091.
- Sarkis-Onofre, R., Cenci, M. S., Demarco, F. F., Lynch, C. D., Fleming, P. S., Pereira-Cenci, T. & Moher, D. 2015. Use of Guidelines to Improve the Quality and Transparency of Reporting Oral Health Research. *Journal of Dentistry*, 43(4), 397-404.
- Schiro, A. & Stein, D. J. 2015. Why Can't I Just Stay on Prednisone? The Long-Term Adverse Effects of Steroids. *Inflammatory Bowel Disease*. Springer.
- Schoepfer, A. M., Dehlavi, M.-A., Fournier, N., Safroneeva, E., Straumann, A., Pittet, V., Peyrin-Biroulet, L., Michetti, P., Rogler, G. & Vavricka, S. R. 2013. Diagnostic Delay in Crohn's Disease Is

Associated with a Complicated Disease Course and Increased Operation Rate. *The American Journal of Gastroenterology*, 108(11), 1744.

- Scholten, A.-M., Vermeulen, E., Dhonukshe-Rutten, R. a. M., Verhagen, T., Visscher, A., Olivier, A., Timmer, L. & Witteman, B. J. M. 2017. Surplus Vitamin B12 Use Does Not Reduce Fatigue in Patients with Irritable Bowel Syndrome or Inflammatory Bowel Disease: A randomized Double-Blind Placebo-Controlled Trial. *Clinical Nutrition*, 23(1), 48-53.
- Schoultz, M., Atherton, I. & Watson, A. 2015. Mindfulness-Based Cognitive Therapy for Inflammatory Bowel Disease Patients: Findings from an Exploratory Pilot Randomised Controlled Trial. *Trials*, 16(1), 378-390.
- Schoultz, M., Macaden, L. & Watson, A. J. M. 2016. Co-Designing Inflammatory Bowel Disease (Ibd) Services in Scotland: Findings from a Nationwide Survey. *BMC Health Services Research*, 16(1), 231-240.
- Schroeder, K. W., Tremaine, W. J. & Ilstrup, D. M. 1987. Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis. *New England Journal of Medicine*, 317(26), 1625-1629.
- Schulz, K. F., Altman, D. G. & Moher, D. 2010. Consort 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *British Medical Journal*, 340(8), 1.
- Schwartz, A. L. 2000. Daily Fatigue Patterns and Effect of Exercise in Women with Breast Cancer. *Cancer Practice*, 8(1), 16-24.
- Sedgwick, P. 2014. Cross Sectional Studies: Advantages and Disadvantages. *British Medical Journal*, 348(2276), 1.
- Seyyedrasooli, A., Parvan, K., Rahmani, A. & Rahimi, Z. 2013. Effect of Illness Perception Promoting Interventions on Treatment Adherence in Hemodialysis Patients: A Randomized Controlled Trial. *Journal of Critical Care Nursing*, 6(2), 81-90.
- Shamseer, L., Hopewell, S., Altman, D. G., Moher, D. & Schulz, K. F. 2016. Update on the Endorsement of Consort by High Impact Factor Journals: A Survey of Journal "Instructions to Authors" in 2014. *Trials*, 17(1), 301.
- Shanyinde, M., Pickering, R. M. & Weatherall, M. 2011. Questions Asked and Answered in Pilot and Feasibility Randomized Controlled Trials. *BMC Medical Research Methodology*, 11(1), 117.
- Shen, J., Barbera, J. & Shapiro, C. M. 2006. Distinguishing Sleepiness and Fatigue: Focus on Definition and Measurement. *Sleep Medicine Reviews*, 10(1), 63-76.
- Shortell, S. M., Marsteller, J. A., Lin, M., Pearson, M. L., Wu, S.-Y., Mendel, P., Cretin, S. & Rosen, M. 2004. The Role of Perceived Team Effectiveness in Improving Chronic Illness Care. *Medical care*, 42(11), 1040-1048.
- Siegel, C., Spiegel, B., Whitman, C., Feagan, B., Sands, B., Loftus, E., Panaccione, R., D'haens, G., Bernstein, C. & Gearry, R. 2016a. Looking Beyond Symptoms and Disease Activity to Define Disease Severity in Inflammatory Bowel Disease: Results of an Ioibd Specialist Panel. *Journal of Crohn's & Colitis*, 10(S1), S76-S78.

- Siegel, C. A., Whitman, C. B., Feagan, B., Spiegel, B. M., Sands, B., Loftus, E. V., Panaccione, R., D'haens, G., Bernstein, C. N. & Gearry, R. 2016b. Development of an Index to Define Overall Disease Severity in Ibd. *Gut*, 67(1), 244-254.
- Siemonsma, P. C., Schröder, C. D., Roorda, L. D. & Lettinga, A. T. 2010. Benefits of Treatment Theory in the Design of Explanatory Trials: Cognitive Treatment of Illness Perceptions in Chronic Low Back Pain Rehabilitation as an Illustrative Example. *Journal of rehabilitation medicine*, 42(2), 111-116.
- Silverberg, M. S., Satsangi, J., Ahmad, T., Arnott, I. D., Bernstein, C. N., Brant, S. R., Caprilli, R., Colombel, J.-F., Gasche, C. & Geboes, K. 2005. Toward an Integrated Clinical, Molecular and Serological Classification of Inflammatory Bowel Disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Canadian Journal of Gastroenterology and Hepatology*, 19(SA), 5A-36A.
- Simera, I., Moher, D., Hoey, J., Schulz, K. F. & Altman, D. G. 2010. A Catalogue of Reporting Guidelines for Health Research. *European Journal of Clinical Investigation*, 40(1), 35-53.
- Singh, H., Arya, S., Talapatra, P., Lather, K., Mathur, R., Singhanian, A. & Chaudhary, V. 2014. Assessment of Fatigue in Rheumatoid Arthritis (by Functional Assessment of Chronic Illness Therapy–Fatigue Score) and Its Relation to Disease Activity and Anemia. *JCR: Journal of Clinical Rheumatology*, 20(2), 87-90.
- Singh, J. A., Wells, G. A., Christensen, R., Tanjong Ghogomu, E., Maxwell, L. J., Macdonald, J. K., Filippini, G., Skoetz, N., Francis, D. K. & Lopes, L. C. 2011a. Adverse Effects of Biologics: A Network Meta-Analysis and Cochrane Overview. *The Cochrane Library*.
- Singh, S., Blanchard, A., Walker, J. R., Graff, L. A., Miller, N. & Bernstein, C. N. 2011b. Common Symptoms and Stressors among Individuals with Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology*, 9(9), 769-775.
- Sirois, F. M. 2009. Psychological Adjustment to Inflammatory Bowel Disease: The Importance of Considering Disease Activity. *The American Journal of Gastroenterology*, 104(12), 2970-2972.
- Skerrett, T. N. & Moss-Morris, R. 2006. Fatigue and Social Impairment in Multiple Sclerosis: The Role of Patients' Cognitive and Behavioral Responses to Their Symptoms. *Journal of Psychosomatic Research*, 61(5), 587-593.
- Slobogean, G. P., Verma, A., Giustini, D., Slobogean, B. L. & Mulpuri, K. 2009. Medline, Embase, and Cochrane Index Most Primary Studies but Not Abstracts Included in Orthopedic Meta-Analyses. *Journal of Clinical Epidemiology*, 62(12), 1261-1267.
- Smets, E., Garssen, B., Bonke, B. D. & De Haes, J. 1995. The Multidimensional Fatigue Inventory (Mfi) Psychometric Qualities of an Instrument to Assess Fatigue. *Journal of Psychosomatic Research*, 39(3), 315-325.
- Smith, K. A., Cipriani, A. & Geddes, J. R. 2016. The Usefulness and Interpretation of Systematic Reviews. *BJPsych Advances*, 22(2), 132-141.
- Smith, S. M., Murchie, P., Devereux, G., Johnston, M., Lee, A. J. & Macleod, U. 2012. Developing a Complex Intervention to Reduce Time to Presentation with Symptoms of Lung Cancer. *British Journal of General Practice*, 62(602), 605-615.

- Smith, S. S., Oei, T. P., Douglas, J. A., Brown, I., Jorgensen, G. & Andrews, J. 2008. Confirmatory Factor Analysis of the Epworth Sleepiness Scale (Ess) in Patients with Obstructive Sleep Apnoea. *Sleep Medicine*, 9(7), 739-744.
- Snaith, R. P. 2003. The Hospital Anxiety and Depression Scale. *Health and Quality of Life Outcomes*, 1(1), 29.
- Solberg, I. C., Lygren, I., Jahnsen, J., Aadland, E., Høie, O., Cvancarova, M., Bernklev, T., Henriksen, M., Sauar, J. & Vatn, M. H. 2009. Clinical Course During the First 10 Years of Ulcerative Colitis: Results from a Population-Based Inception Cohort (Ibsen Study). *Scandinavian Journal of Gastroenterology*, 44(4), 431-440.
- Spence, M. J. & Moss-Morris, R. 2007. The Cognitive Behavioural Model of Irritable Bowel Syndrome: A Prospective Investigation of Patients with Gastroenteritis. *Gut*, 56(8), 1066-1071.
- Spitzer, R. L., Kroenke, K., Williams, J. B. & Löwe, B. 2006. A Brief Measure for Assessing Generalized Anxiety Disorder: The Gad-7. *Archives of Internal Medicine*, 166(10), 1092-1097.
- Spurio, F. F., Aratari, A., Margagnoni, G., Doddato, M. T. & Papi, C. 2012. Early Treatment in Crohn's Disease: Do We Have Enough Evidence to Reverse the Therapeutic Pyramid? *Journal of Gastrointestinal Liver Diseases*, 21(1), 67-73.
- Stableford, S. & Mettger, W. 2007. Plain Language: A Strategic Response to the Health Literacy Challenge. *Journal of Public Health Policy*, 28(1), 71-93.
- Stallmach, A., Hagel, S. & Bruns, T. 2010. Adverse Effects of Biologics Used for Treating Ibd. *Best Practice & Research Clinical Gastroenterology*, 24(2), 167-182.
- Stange, E., Travis, S., Vermeire, S., Reinisch, W., Geboes, K., Barakauskiene, A., Feakins, R., Fléjou, J., Herfarth, H. & Hommes, D. 2008. European Evidence-Based Consensus on the Diagnosis and Management of Ulcerative Colitis: Definitions and Diagnosis. *Journal of Crohn's and Colitis*, 2(1), 1-23.
- Staples, M. & Niazi, M. 2007. Experiences Using Systematic Review Guidelines. *Journal of Systems and Software*, 80(9), 1425-1437.
- Stevens, A., Shamseer, L., Weinstein, E., Yazdi, F., Turner, L., Thielman, J., Altman, D. G., Hirst, A., Hoey, J., Palepu, A., Schulz, K. F. & Moher, D. 2014. Relation of Completeness of Reporting of Health Research to Journals' Endorsement of Reporting Guidelines: Systematic Review. *British Medical Journal*, 348(1), 1-29.
- Stevens, B. W., Borren, N. Z., Velonias, G., Conway, G., Cleland, T., Andrews, E., Khalili, H., Garber, J. G., Xavier, R. J., Yajnik, V. & Ananthakrishnan, A. N. 2017. Vedolizumab Therapy Is Associated with an Improvement in Sleep Quality and Mood in Inflammatory Bowel Diseases. *Digestive Diseases and Sciences*, 62(1), 197-206.
- Stidham, R., Lee, T., Higgins, P., Deshpande, A., Sussman, D., Singal, A., Elmunzer, B., Saini, S., Vijan, S. & Waljee, A. 2014a. Systematic Review with Network Meta-Analysis: The Efficacy of Anti-Tnf Agents for the Treatment of Crohn's Disease. *Alimentary Pharmacology & Therapeutics*, 39(12), 1349-1362.
- Stidham, R., Lee, T., Higgins, P., Deshpande, A. R., Sussman, D. A., Singal, A., Elmunzer, B., Saini, S., Vijan, S. & Waljee, A. 2014b. Systematic Review with Network Meta-Analysis: The Efficacy of

Anti-Tumour Necrosis Factor-Alpha Agents for the Treatment of Ulcerative Colitis. *Alimentary Pharmacology & Therapeutics*, 39(7), 660-671.

- Stiles-Shields, C., Kwasny, M. J., Cai, X. & Mohr, D. C. 2014. Therapeutic Alliance in Face-to-Face and Telephone-Administered Cognitive Behavioral Therapy. *Journal of Consulting and Clinical Psychology*, 82(2), 349-354.
- Stone, A. A., Schwartz, J. E., Broderick, J. E. & Shiffman, S. S. 2005. Variability of Momentary Pain Predicts Recall of Weekly Pain: A Consequence of the Peak (or Salience) Memory Heuristic. *Personality and Social Psychology Bulletin*, 31(10), 1340-1346.
- Stone, C. D. 2012. The Economic Burden of Inflammatory Bowel Disease: Clear Problem, Unclear Solution. *Digestive Diseases and Sciences*, 57(12), 1-3.
- Stover, A. M., Reeve, B. B., Piper, B. F., Alfano, C. M., Smith, A. W., Mitchell, S. A., Bernstein, L., Baumgartner, K. B., Mctiernan, A. & Ballard-Barbash, R. 2013. Deriving Clinically Meaningful Cut-Scores for Fatigue in a Cohort of Breast Cancer Survivors: A Health, Eating, Activity, and Lifestyle (Heal) Study. *Quality of Life Research*, 22(9), 2279-2292.
- Sturm, A., Maaser, C., Mendall, M., Karagiannis, D., Karatzas, P., Ipenburg, N., Sebastian, S., Rizzello, F., Limdi, J. & Katsanos, K. 2016. European Crohn's and Colitis Organisation Topical Review on Ibd in the Elderly. *Journal of Crohn's and Colitis*, 11(3), 263-273.
- Sturt, J., Dennick, K., Due-Christensen, M. & Mccarthy, K. 2015. The Detection and Management of Diabetes Distress in People with Type 1 Diabetes. *Current Diabetes Reports*, 15(11), 101.
- Sturt, J., Whitlock, S. & Hearnshaw, H. 2006. Complex Intervention Development for Diabetes Self-Management. *Journal of Advanced Nursing*, 54(3), 293-303.
- Suarez-Almazor, M. E., Belseck, E., Homik, J., Dorgan, M. & Ramos-Remus, C. 2000. Identifying Clinical Trials in the Medical Literature with Electronic Databases: Medline Alone Is Not Enough. *Controlled Clinical Trials*, 21(5), 476-487.
- Sutton, A. J., Cooper, N. J. & Jones, D. R. 2009. Evidence Synthesis as the Key to More Coherent and Efficient Research. *BMC Medical Research Methodology*, 9(1), 29-41.
- Szigethy, E., Mcauliff, K., Strassburger, M., Hashash, J., Vachon, A., Rode, N. M., Keljo, D. J., Youk, A. O., Regueiro, M. & Binion, D. 2016. 6.20 Brief Behavioral Therapy and Bupropion for Sleep and Fatigue in Adolescents and Young Adults with Inflammatory Bowel Disease. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(10), S210.
- Targownik, L. E., Sexton, K. A., Bernstein, M. T., Beatie, B., Sargent, M., Walker, J. R. & Graff, L. A. 2015. The Relationship among Perceived Stress, Symptoms, and Inflammation in Persons with Inflammatory Bowel Disease. *The American Journal of Gastroenterology*, 110(7), 1001-1012.
- Tarquinio, C., Kivits, J., Minary, L., Coste, J. & Alla, F. 2015. Evaluating Complex Interventions: Perspectives and Issues for Health Behaviour Change Interventions. *Psychology & Health*, 30(1), 35-51.
- Tate, D. F., Lytle, L. A., Sherwood, N. E., Haire-Joshu, D., Matheson, D., Moore, S. M., Loria, C. M., Pratt, C., Ward, D. S., Belle, S. H. & Michie, S. 2016. Deconstructing Interventions: Approaches to Studying Behavior Change Techniques across Obesity Interventions. *Translational Behavioral Medicine*, 6(2), 236-243.

- Taylor, N. J., Sahota, P., Sargent, J., Barber, S., Loach, J., Louch, G. & Wright, J. 2013. Using Intervention Mapping to Develop a Culturally Appropriate Intervention to Prevent Childhood Obesity: The Happy (Healthy and Active Parenting Programme for Early Years) Study. *International Journal of Behavioral Nutrition and Physical Activity*, 10(1), 142.
- Tew, G. A., Jones, K. & Mikocka-Walus, A. 2016. Physical Activity Habits, Limitations, and Predictors in People with Inflammatory Bowel Disease: A Large Cross-Sectional Online Survey. *Inflammatory Bowel Diseases*, 22(12), 2933-2942.
- Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., Robson, R., Thabane, M., Giangregorio, L. & Goldsmith, C. H. 2010. A Tutorial on Pilot Studies: The What, Why and How. *BMC Medical Research Methodology*, 10(1), 1.
- Thomas, P. W., Thomas, S., Kersten, P., Jones, R., Slingsby, V., Nock, A., Smith, A. D., Baker, R., Galvin, K. T. & Hillier, C. 2014. One Year Follow-up of a Pragmatic Multi-Centre Randomised Controlled Trial of a Group-Based Fatigue Management Programme (Facets) for People with Multiple Sclerosis. *BMC Neurology*, 14(1), 1-10.
- Tian, J. & Hong, J.-S. 2013. Application of the Chinese Version of the Mfi-20 in Detecting the Severe Fatigue in Cancer Patients. *Supportive Care in Cancer*, 21(8), 2217-2223.
- Tickle-Degnen, L. 2013. Nuts and Bolts of Conducting Feasibility Studies. *The American Journal of Occupational Therapy*, 67(2), 171-176.
- Timmer, A., Patton, P. H., Chande, N., McDonald, J. W. & Macdonald, J. K. 2016. Azathioprine and 6-Mercaptopurine for Maintenance of Remission in Ulcerative Colitis. *The Cochrane Library*.
- Timmer, A., Preiss, J. C., Motschall, E., Rücker, G., Jantschek, G. & Moser, G. 2011. Psychological Interventions for Treatment of Inflammatory Bowel Disease. *The Cochrane Database of Systematic Reviews*.
- Titov, N., Dear, B. F., Mcmillan, D., Anderson, T., Zou, J. & Sunderland, M. 2011. Psychometric Comparison of the Phq-9 and Bdi-Ii for Measuring Response During Treatment of Depression. *Cognitive Behaviour Therapy*, 40(2), 126-136.
- To, N., Ford, A. & Gracie, D. 2016a. Systematic Review with Meta-Analysis: The Adverse Effects of Tobacco Smoking on the Natural History of Crohn's Disease. *Alimentary Pharmacology & Therapeutics*, 43(5), 549-561.
- To, N., Gracie, D. & Ford, A. 2016b. Systematic Review with Meta-Analysis: The Effect of Tobacco Smoking on the Natural History of Ulcerative Colitis. *Alimentary Pharmacology & Therapeutics*, 44(2), 117-126.
- Tougas, M. E., Hayden, J. A., McGrath, P. J., Huguet, A. & Rozario, S. 2015. A Systematic Review Exploring the Social Cognitive Theory of Self-Regulation as a Framework for Chronic Health Condition Interventions. *PLOS One*, 10(8), e0134977.
- Turner, L., Shamseer, L., Altman, D., Weeks, L., Peters, J., Kober, T., Dias, S., Schulz, K., Plint, A. & Moher, D. 2011. Consolidated Standards of Reporting Trials (Consort) and the Completeness of Reporting of Randomised Controlled Trials (Rcts) Published in Medical Journals. *The Cochrane Database of Systematic Reviews*.

- Turner, L., Shamseer, L., Altman, D. G., Schulz, K. F. & Moher, D. 2012. Does Use of the Consort Statement Impact the Completeness of Reporting of Randomised Controlled Trials Published in Medical Journals? A Cochrane Review. *Systematic Reviews*, 1(1), 60-69.
- Van Assche, G., Dignass, A., Panes, J., Beaugerie, L., Karagiannis, J., Allez, M., Ochsenaühn, T., Orchard, T., Rogler, G. & Louis, E. 2010. The Second European Evidence-Based Consensus on the Diagnosis and Management of Crohn's Disease: Definitions and Diagnosis. *Journal of Crohn's and Colitis*, 4(1), 7-27.
- Van Den Haak, M. J., De Jong, M. D. & Schellens, P. J. 2007. Evaluation of an Informational Web Site: Three Variants of the Think-Aloud Method Compared. *Technical Communication*, 54(1), 58-71.
- Van Den Heuvel, T. R., Jeurig, S. F., Zeegers, M. P., Van Dongen, D. H., Wolters, A., Masclee, A. A., Hameeteman, W. H., Romberg-Camps, M. J., Oostenbrug, L. E. & Pierik, M. J. 2017. A 20-Year Temporal Change Analysis in Incidence, Presenting Phenotype and Mortality, in the Dutch Ibdsl Cohort—Can Diagnostic Factors Explain the Increase in Ibd Incidence? *Journal of Crohn's and Colitis*, 11(10), 1169-1179.
- Van Der Have, M., Fidder, H. H., Leenders, M., Kaptein, A. A., Van Der Valk, M. E., Van Bodegraven, A. A., Dijkstra, G., De Jong, D. J., Pierik, M. & Ponsioen, C. Y. 2015. Self-Reported Disability in Patients with Inflammatory Bowel Disease Largely Determined by Disease Activity and Illness Perceptions. *Inflammatory Bowel Diseases*, 21(2), 369-377.
- Van Der Have, M., Oldenburg, B., Kaptein, A. A., Jansen, J. M., Scheffer, R. C., Van Tuyl, B. A., Van Der Meulen-De, A. E., Pierik, M., Siersema, P. D. & Van Oijen, M. G. 2016. Non-Adherence to Anti-Tnf Therapy Is Associated with Illness Perceptions and Clinical Outcomes in Outpatients with Inflammatory Bowel Disease: Results from a Prospective Multicentre Study. *Journal of Crohn's and Colitis*, 10(5), 549-555.
- Van Der Sloot, K. W., Amini, M., Peters, V., Dijkstra, G. & Alizadeh, B. Z. 2017. Inflammatory Bowel Diseases: Review of Known Environmental Protective and Risk Factors Involved. *Inflammatory Bowel Diseases*, 23(9), 1499-1509.
- Van Erp, S., Vollmann, M., Van Der Heijde, D., Veenendaal, R. A., Brakenhoff, L. K. M. P., Fidder, H. H., Hommes, D. W., Kaptein, A. A., Van Der Meulen-De Jong, A. E. & Scharloo, M. 2017. Illness Perceptions and Outcomes in Patients with Inflammatory Bowel Disease: Is Coping a Mediator? *International Journal of Behavioral Medicine*, 24(2), 205-214.
- Van Kessel, K. & Moss-Morris, R. 2006. Understanding Multiple Sclerosis Fatigue: A Synthesis of Biological and Psychological Factors. *Journal of Psychosomatic Research*, 61(5), 583-585.
- Van Kessel, K., Moss-Morris, R., Willoughby, E., Chalder, T., Johnson, M. H. & Robinson, E. 2008. A Randomized Controlled Trial of Cognitive Behavior Therapy for Multiple Sclerosis Fatigue. *Psychosomatic Medicine*, 70(2), 205-213.
- Van Kessel, K., Woules, T. & Moss-Morris, R. 2016. A New Zealand Pilot Randomized Controlled Trial of a Web-Based Interactive Self-Management Programme (Msinvigor8) with and without Email Support for the Treatment of Multiple Sclerosis Fatigue. *Clinical Rehabilitation*, 30(5), 454-462.
- Van Langenberg, D. & Gibson, P. 2010. Systematic Review: Fatigue in Inflammatory Bowel Disease. *Alimentary Pharmacology & Therapeutics*, 32(2), 131-143.

- Van Langenberg, D. R. & Gibson, P. R. 2014. Factors Associated with Physical and Cognitive Fatigue in Patients with Crohn's Disease: A Cross-Sectional and Longitudinal Study. *Inflammatory Bowel Diseases*, 20(1), 115-125.
- Van Oostrom, S. H., Anema, J. R., Terluin, B., Venema, A., De Vet, H. C. & Van Mechelen, W. 2007. Development of a Workplace Intervention for Sick-Listed Employees with Stress-Related Mental Disorders: Intervention Mapping as a Useful Tool. *BMC Health Services Research*, 7(1), 127.
- Van Teijlingen, E. & Hundley, V. 2001. The Importance of Pilot Studies. *Social Research Update*, 35), 1-4.
- Van Teijlingen, E. R., Rennie, A. M., Hundley, V. & Graham, W. 2001. The Importance of Conducting and Reporting Pilot Studies: The Example of the Scottish Births Survey. *Journal of Advanced Nursing*, 34(3), 289-295.
- Van't Leven, M., Zielhuis, G. A., Van Der Meer, J. W., Verbeek, A. L. & Bleijenberg, G. 2010. Fatigue and Chronic Fatigue Syndrome-Like Complaints in the General Population*. *European Journal of Public Health*, 20(3), 251-257.
- Vermeire, S., Schreiber, S., Sandborn, W. J., Dubois, C. & Rutgeerts, P. 2010. Correlation between the Crohn's Disease Activity and Harvey–Bradshaw Indices in Assessing Crohn's Disease Severity. *Clinical Gastroenterology and Hepatology*, 8(4), 357-363.
- Vestergaard, C., Dahlerup, J. F. & Bager, P. 2017. Validation of the Danish Version of Inflammatory Bowel Disease Self-Assessment Scale. *Danish Medical Journal*, 64(8), 1-10.
- Victora, C. G., Habicht, J.-P. & Bryce, J. 2004. Evidence-Based Public Health: Moving Beyond Randomized Trials. *American Journal of Public Health*, 94(3), 400-405.
- Vogelaar, L., Van't Spijker, A., Timman, R., Van Tilburg, A. J., Bac, D., Vogelaar, T., Kuipers, E. J., Van Busschbach, J. J. & Van Der Woude, C. J. 2014. Fatigue Management in Patients with Ibd: A Randomised Controlled Trial. *Gut*, 63(6), 911-918.
- Vogelaar, L., Van't Spijker, A., Vogelaar, T., Van Busschbach, J. J., Visser, M. S., Kuipers, E. J. & Van Der Woude, C. J. 2011. Solution Focused Therapy: A Promising New Tool in the Management of Fatigue in Crohn's Disease Patients: Psychological Interventions for the Management of Fatigue in Crohn's Disease. *Journal of Crohn's and Colitis*, 5(6), 585-591.
- Walker, J. R., Ediger, J. P., Graff, L. A., Greenfeld, J. M., Clara, I., Lix, L., Rawsthorne, P., Miller, N., Rogala, L. & Mcphail, C. M. 2008. The Manitoba Ibd Cohort Study: A Population-Based Study of the Prevalence of Lifetime and 12-Month Anxiety and Mood Disorders. *The American Journal of Gastroenterology*, 103(8), 1989-1997.
- Walmsley, R., Ayres, R., Pounder, R. & Allan, R. 1998. A Simple Clinical Colitis Activity Index. *Gut*, 43(1), 29-32.
- Wang, S., Moss, J. R. & Hiller, J. E. 2006. Applicability and Transferability of Interventions in Evidence-Based Public Health. *Health Promotion International*, 21(1), 76-83.
- Waters, E., Hall, B., Armstrong, R., Doyle, J., Pettman, T. & De Silva-Sanigorski, A. 2011. Essential Components of Public Health Evidence Reviews: Capturing Intervention Complexity, Implementation, Economics and Equity. *Journal of Public Health*, 33(3), 462-465.

- Wearden, A. J. & Emsley, R. 2013. Mediators of the Effects on Fatigue of Pragmatic Rehabilitation for Chronic Fatigue Syndrome. *Journal of Consulting and Clinical Psychology*, 81(5), 831-840.
- Weinman, J., Petrie, K. J., Moss-Morris, R. & Horne, R. 1996. The Illness Perception Questionnaire: A New Method for Assessing the Cognitive Representation of Illness. *Psychology & Health*, 11(3), 431-445.
- Wells, M., Williams, B., Treweek, S., Coyle, J. & Taylor, J. 2012. Intervention Description Is Not Enough: Evidence from an in-Depth Multiple Case Study on the Untold Role and Impact of Context in Randomised Controlled Trials of Seven Complex Interventions. *Trials*, 13(1), 96-105.
- Westen, D., Novotny, C. M. & Thompson-Brenner, H. 2004. The Empirical Status of Empirically Supported Psychotherapies: Assumptions, Findings, and Reporting in Controlled Clinical Trials. *Psychological Bulletin*, 130(4), 631.
- Westlund, E. & Stuart, E. A. 2016. The Nonuse, Misuse, and Proper Use of Pilot Studies in Experimental Evaluation Research. *American Journal of Evaluation*, 38(2), 246-261.
- Whitehead, A. L., Sully, B. G. & Campbell, M. J. 2014. Pilot and Feasibility Studies: Is There a Difference from Each Other and from a Randomised Controlled Trial? *Contemporary Clinical Trials*, 38(1), 130-133.
- Whitehead, L. 2009. The Measurement of Fatigue in Chronic Illness: A Systematic Review of Unidimensional and Multidimensional Fatigue Measures. *Journal of Pain and Symptom Management*, 37(1), 107-128.
- Whitehead, L. C., Unahi, K., Burrell, B. & Crowe, M. T. 2016. The Experience of Fatigue across Long-Term Conditions: A Qualitative Meta-Synthesis. *Journal of Pain and Symptom Management*, 52(1), 131-143.
- Wieseler, B., Wolfram, N., McGauran, N., Kerekes, M. F., Vervolgyi, V., Kohlepp, P., Kamphuis, M. & Grouven, U. 2013. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. *PLoS Med*, 10(10), 37-50.
- Wight, D., Wimbush, E., Jepson, R. & Doi, L. 2015. Six Steps in Quality Intervention Development (6squad). *Journal of Epidemiology and Community Health*, 70(5), 520-526.
- Wilburn, J., Twiss, J., Kemp, K. & McKenna, S. P. 2017. A Qualitative Study of the Impact of Crohn's Disease from a Patient's Perspective. *Frontline Gastroenterology*, 8(1), 68-73.
- Williams, C. & Garland, A. 2002. A Cognitive-Behavioural Therapy Assessment Model for Use in Everyday Clinical Practice. *Advances in Psychiatric Treatment*, 8(3), 172-179.
- Williet, N., Sarter, H., Gower-Rousseau, C., Adrianjafy, C., Olympie, A., Buisson, A., Beaugerie, L. & Peyrin-Biroulet, L. 2016. Patient Reported-Outcomes in a French Nationwide Survey of Inflammatory Bowel Disease Patients. *Journal of Crohn's and Colitis*, 11(2), 165-174.
- Wilson, D. T., Walwyn, R. E. A., Brown, J., Farrin, A. J. & Brown, S. R. 2015. Statistical Challenges in Assessing Potential Efficacy of Complex Interventions in Pilot or Feasibility Studies. *Statistical Methods in Medical Research*, 25(3), 997-1009.

- Windgassen, S., Goldsmith, K., Moss-Morris, R. & Chalder, T. 2016. Establishing How Psychological Therapies Work: The Importance of Mediation Analysis. *Journal of Mental Health*, 25(2), 93-100.
- Wong, S. S., Wilczynski, N. L. & Haynes, R. B. 2006. Comparison of Top-Performing Search Strategies for Detecting Clinically Sound Treatment Studies and Systematic Reviews in Medline and Embase. *Journal of the Medical Library Association*, 94(4), 451.
- Woodward, S., Dibley, L., Coombes, S., Bellamy, A., Clark, C., Czuber-Dochan, W., Everelm, L., Kutner, S., Sturt, J. & Norton, C. 2016. Identifying Disease-Specific Distress in Patients with Inflammatory Bowel Disease. *British Journal of Nursing*, 25(1), 649-60.
- Yamaguchi, S., Takeuchi, Y., Arai, K., Fukuda, K., Kuroki, Y., Asonuma, K., Takahashi, H., Saruta, M. & Yoshida, H. 2016. Fecal Calprotectin Is a Clinically Relevant Biomarker of Mucosal Healing in Patients with Quiescent Ulcerative Colitis. *Journal of Gastroenterology and Hepatology*, 31(1), 93-98.
- Yan, J., You, L.-M., Liu, B.-L., Jin, S.-Y., Zhou, J.-J., Lin, C.-X., Li, Q. & Gu, J. 2014. The Effect of a Telephone Follow-up Intervention on Illness Perception and Lifestyle after Myocardial Infarction in China: A Randomized Controlled Trial. *International Journal of Nursing Studies*, 51(6), 844-855.
- Yang, H., Mcelree, C., Roth, M., Shanahan, F., Targan, S. & Rotter, J. 1993. Familial Empirical Risks for Inflammatory Bowel Disease: Differences between Jews and Non-Jews. *Gut*, 34(4), 517-524.
- Yardley, L., Morrison, L., Bradbury, K. & Muller, I. 2015. The Person-Based Approach to Intervention Development: Application to Digital Health-Related Behavior Change Interventions. *Journal of Medical Internet Research*, 17(1), 1-30.
- Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C. & Kaplan, E. 1997. Measuring Fatigue and Other Anemia-Related Symptoms with the Functional Assessment of Cancer Therapy (Fact) Measurement System. *Journal of Pain and Symptom Management*, 13(2), 63-74.
- Zand, A., Van Deen, W. K., Inserra, E. K., Hall, L., Kane, E., Centeno, A., Choi, J. M., Ha, C. Y., Esrailian, E. & D'haens, G. R. 2015. Presenteeism in Inflammatory Bowel Diseases: A Hidden Problem with Significant Economic Impact. *Inflammatory Bowel Diseases*, 21(7), 1623-1630.
- Zhao, F., Suhonen, R., Koskinen, S. & Leino-Kilpi, H. 2016. Theory-Based Self-Management Educational Interventions on Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Advanced Nursing*, 73(4), 812-833.
- Zigmond, A. S. & Snaith, R. P. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, 67(6), 361-370.

9 Appendices

Appendix I: PhD Paper 1 Supplementary Table 1

Characteristics of included studies ($n = 43$).

First Author (Year of publication)	Aims of the study	Design	Sample	Fatigue tool(s)	Main Findings	Study Quality
Pharmacological and non-pharmacological intervention studies						
Costantini (2013) (58)	To assess effectiveness of 1200 mg/day thiamine administered orally or parenterally	Open label pilot study	12 (8 UC/4 CD)	CFS Scale	- Ten/12 patients showed complete regression of fatigue (score 0); 2/12 nearly complete regression of fatigue (score 3 & 5). One patient treated with 1200 mg/day of thiamine showed a mild tachycardia that completely regressed by reducing the dose to 900 mg/day	Low
Garcia-Vega & Fernandez-Rodriguez (2004) (56)	To assess effectiveness of stress management technique in reducing disease activity and improving psychosocial functioning in CD patients	RCT	45 CD	-Semi-structured protocol designed by the authors	- The self-directed stress management reported as significantly reducing tiredness post-treatment and at 6 and 12 months post-treatment - Medical treatment plus psychological treatment seems to be more effective than medical treatment alone	Med
Lichtenstein (2002) (43)	Assess effect of infliximab on quality of life in patients with active CD	RCT, double-blinded	83 CD	-IBDQ	- Placebo and actively treated patients reported symptom improvement - Infliximab improved quality of life and decreased feelings of fatigue	Low
Loftus (2008) (45)	Evaluate effects of adalimumab maintenance therapy on HRQoL in patients with moderate to severe CD	RCT double-blinded	854 CD	FACIT-F IBDQ SF-36	- At baseline patients' mean fatigue scores were 22.9 points - Adalimumab reduced symptoms of fatigue and depression in patients with IBD	Med
Minderhoud (2007) (44)	Measure effect of infliximab on fatigue, clinical disease activity and depression scores	RCT, single blinded	14 CD	MFI IBDQ	- Baseline fatigue prevalence 86% - Fatigue was significantly reduced by administration of a single dose of infliximab (patients with fistulae received one extra dose of infliximab 4 weeks after baseline)	Low
McNelly (2015) (49)	To test effects of (i) individual advice to increase physical activity (PA) and/or (ii) supplementation with omega-3 on fatigue in IBD	RCT, 2x2 factorial study	74 IBD randomised, 60 started, 52 completed the intervention	FACIT-F IBD-F	- There was a significant deterioration in FACIT-F score with the supplementation of omega-3 fish oil - There was no significant difference on FACIT-F scores between those receiving and not receiving exercise advice. Fatigue was significantly reduced in the exercise groups, measured by IBD-F score	Med

Vogelaar (2011) (18)	To assess feasibility and effect of psychological interventions in the management of fatigue	RCT, pilot study	29 CD	CIS	-SFT: fatigue level improved in 6/10 patients, in PST group - 3 of patients improved fatigue scores, and in the CAU group – 3/7 patients improved fatigue from baseline to 3 months follow up -SFT had a positive effect on fatigue, better quality of life and fewer visits to the outpatient clinic	Med
Vogelaar (2014) (17)	To assess effectiveness of SFT compared with CAU on fatigue and QoL in individuals with IBD fatigue	RCT	98 (40 UC/58 CD)	CIS-fatigue	-At 3 and 6 months, scores were significantly better in the SFT group than in the CAU group. Significantly more individuals in the SFT group had a CIS-fatigue score below the cut-off point of 35 compared with individuals in the CAU group. The effect was no longer significant at 9 months	High
Longitudinal population based and outpatient studies						
Banovic (2010) (54)	Assess fatigue, disease activity, depression and anxiety, sleep disturbances, and subjective QoL	Longitudinal study	52 CD	MFI	- Age and gender did not influence fatigue Longitudinal data - Disease was inactive and there was no difference in fatigue score - No significant difference between the two visits on the assessments of depression, anxiety, sleep disturbances, and subjective QoL	Low
Graff (2011) (21)	To evaluate psychological and biological factors in relation to fatigue	Population based cohort study	318 CD	MFI	-72% with active and 30% with inactive disease reached (clinical) threshold for fatigue -Disease activity, poor sleep (but not hours of sleep) and perceived stress were associated with elevated fatigue	Med Same study as (14)
Graff (2013) (14)	To assess fatigue longitudinally to determine the course of fatigue in IBD and the contributors to changes in fatigue	Population based cohort study	312 (153 UC, 159 CD)	MFI at 12, 24 months follow-up	Longitudinal data -Fatigue was higher over time when disease was consistently active -Poor sleep quality, distress, and lower psychological well-being, were significantly associated with changes in fatigue over time. Women and those who were younger were more likely to report higher fatigue - Perceived stress was not statistically significant after the Bonferroni correction. CRP and Hb were not associated with fatigue over time	High Same study as (21)
Kapleman et al. (2014) (9)	To evaluate patient-reported outcomes in a cohort of patients with IBD and their associations between disease activity indices and IBD QoL	Longitudinal study Cross-sectional study	10 634 (3945 UC/6689 CD) 2079 patients for the longitudinal analyses	4 items from each 6 PROMIS item banks (including fatigue)	-Shorter disease duration, active disease, prednisone and having a pouch were associated with worse fatigue - Patients with fatigue had significantly lower levels of quality of life Longitudinally patients with worsening disease activity had worse fatigue and those with improving disease had improved fatigue scores. Older patients, men and those with higher education levels reported better outcomes	Med
Romberg-Camps (2010) (52)	To investigate the prevalence and severity of fatigue and the impact on HRQoL	Population based registry prospective study	707 (304 CD/368 UC/35 indeterminate colitis)	MFI SF-36	- MFI-20 dimensions general fatigue and physical fatigue were significantly worse in CD compared to UC and IBDU - Disease activity and anaemia were positively related with the level of fatigue - In CD, patients using medication were significantly more tired than patients using no medication. Gender, age, length of follow-up, anaemia, and the use	High

					of infliximab did not determine the level of fatigue. In UC female gender was associated with higher fatigue scores, resulting in a worse score. Age, length of follow-up, and medication use were unrelated to fatigue	
Van Langenberg (2014a) (13)	To evaluate prevalence and severity of fatigue in CD (compared with UC and healthy controls) and to identify potentially modifiable factors associated with fatigue	Cohort study Cross-sectional study	311 (113 UC/181 CD/85 HC) at baseline 86 CD individuals at follow-up	FIS at baseline and follow-up for CD individuals, median time = 540	- Current corticosteroid, immunomodulator and biologics were significantly associated with higher fatigue scores. In CD disease activity was associated with fatigue Multivariate logistic regression analyses - Current active, sleep quality, depression, limited employment, smoking and vitamin B group supplement use were associated with fatigue - Small magnitudes of change were observed, mean changes in score = + 0.9 for total fatigue	High
Vogelaar (2013) (36)	To explore frequency of fatigue in two different hospitals, explore the factors related to the risk for fatigue, and investigate differences between disease phenotype in CD patients of a referral hospital and a general hospital	Longitudinal study	425 CD patients	CIS-fatigue	-Patients in disease remission were less fatigued compared to patients with active disease Follow-up multivariate analyses - Women were significantly more fatigued than men. A longer disease duration was associated with significantly less fatigue for men. More disease activity was associated with more fatigue. Patients using 5-ASA at baseline showed less fatigue, but when 5-ASA caused side-effects, fatigue levels were higher at baseline - Anti-TNF use at baseline associated with a higher fatigue level, maintaining anti-TNF through the follow-up year associated with a decreased fatigue levels: this levels was still significantly higher compared with that in a non-anti-TNF users	Med
Cross-sectional studies						
Bager (2012) (28)	To investigate prevalence, characteristics and determinants of fatigue in IBD	Cross-sectional study	437 IBD	MFI	- Fatigue scores were not significantly different between the UC and CD patients. Fatigue was significantly associated with disease activity and age (UC females)	High
Banovic (2012a) (42)	To identify diagnostic variables of IBD-fatigue using the CART method	Cross-sectional study	118 (26 UC/92 CD)	MFI	-Depressive mood, trait-anxiety and daytime sleepiness were the most explanatory variables in patients with fatigue	Med
Banovic (2012b) (50)	To determine relationships between personality and the perception of IBD-fatigue when disease is in remission	Cross-sectional study	135 (22 UC/59 CD)	MFI	- No significant relationship between level of fatigue and duration of disease, number of relapses, number of flare ups, number of quiescent periods, number of hospitalizations Univariate analysis - Significant relationship between level of fatigue and cumulative severity of intestinal resection, anxiety, daytime sleepiness and self-directedness Multivariate analysis - Forty-five percent variance in fatigue (MFI) was explained by the value of PSHI, daytime sleepiness, persistence and self-directness	Low

Bjornsson (2004) (29)	To evaluate well-being in patients with primary sclerosing cholangitis with focus on fatigue in comparison with IBD alone and matched with general population	Cross-sectional study	151 IBD from two hospitals, one in the UK and one in Sweden	FIS	- Fatigue was significantly positively associated with disease activity and depression	Low
Bol (2010) (77)	To study disease specificity of fatigue in multiple sclerosis and comparing its level with UC	Cross-sectional study	76 UC & 88 MS	MFI	- Physical fatigue in both MS and UC patients significantly correlated with disease severity, depression, and negative affectivity, but not with age and gender	Med
Castillo-Cejas et al. (2013) (5)	To define applicability of three questionnaires and to define which had better application characteristics. To determine the impact of fatigue on health perception in patients with IBD	Validation study Cross-sectional study	Validation Phase 99 (44 UC/55 CD) Questionnaire administration Phase 137 (70 CD/67 UC) + 69 HC	DFIS FSS MFIS	Validation phase - There was a significant correlation of QoL with the three fatigue questionnaires. There was a positive significant relationship between the degree of disease activity and the level of fatigue in the three questionnaires Questionnaire administration phase -There were no statistically significant differences between CD and UC. -There was a significant relationship between clinical disease activity and fatigue. There was a significant inverse relationship between fatigue and QoL	Med
Cohen (2014) (6)	To report the prevalence of fatigue in a cohort of newly diagnosed IBD individuals. To explore the relationship of fatigue with QoL, depression and disability	Cross-sectional study	220 (95 UC/125 CD)	FACIT-F	- No significant differences in fatigue prevalence between CD and UC - CD individuals with active disease were significantly more likely to have fatigue than those with inactive disease (not significant in UC). Significantly more women met fatigue criteria than men - Fatigue was significantly associated with disease specific (IBDQ) and general (SF-36, EQ-5D) quality of life -Those with fatigue had significantly worse valuations of their current health state and were significantly more impaired in their daily activities. Working individuals fatigue had significantly higher, overall work impairment, work impairment and absenteeism (CD only). Depression was significantly greater with fatigue than without	Med
Goldenberg (2013) (31)	To investigate the relationship between iron deficiency and fatigue in IBD, in the absence of anaemia	Cross-sectional study	280 (128 UC/137 CD)	MFI	- 49% of individuals with iron deficiency had high fatigue, 45% of individuals without iron deficiency had high fatigue (MFI > 13) -No mean differences in types of fatigue or fatigue outcomes between iron-deficient and iron-sufficient groups. Those with high fatigue had lower mean Hb than those without fatigue, but the difference was not significant. -Fatigue was significantly more likely to occur during active disease	High
Grimstad (2015) (41)	To describe the prevalence and degree of fatigue in newly diagnosed and untreated IBD patients.	Cross-sectional study	81 (60 UC/21 CD) + 67 HCs	FSS and fVAS	Univariate analysis -No significant associations between fatigue and disease activity, CRP or faecal calprotectin. fVAS scores were associated with CRP, ferritin and depression, FSS scores were associated with calprotectin and depression	High

	Explore associations between fatigue, depression and disease activity.				Multivariate analysis - HADS-D and age were significantly associated with fatigue. CRP, ferritin, calprotectin and gender were not significantly associated with fatigue	
Hauser (2005) (46)	To identify determinants of fatigue in IBD-outpatients in remission or with slight disease activity	Secondary data analysis	37 UC with IPAA & 40 UC without ileal pouch-anal anastomosis	GSCL (fatigue subscale), SF-36	-Fatigue had significant predictive value for reduced physical and social functioning. Fatigue in UC patients was independent from objective disease measures in quiescent disease. Disease activity and depression were predictors of fatigue	Low
Jelsness-Jorgensen (2010) (22)	Estimate level and frequency of fatigue among patients with mild to moderate IBD compared with healthy controls	Cross-sectional study	140 IBD patients (UC/CD 92/48) & 2287 healthy controls	FQ IBDQ	- Age, gender, employment, nor education had statistically significant impact on fatigue - IBD symptoms, Hb levels, and altered sleep patterns were significant predictors of chronic fatigue	High
Jelsness-Jorgensen (2011) (7)	To investigate influence of chronic fatigue on generic and disease-specific HRQoL	Cross-sectional study	140 IBD (UC/CD 92/48)	FQ SF-36 IBDQ	- Fatigue was associated with increased IBD symptoms, smoking and Hb values, reduced scores in general health and HQoL	Same study as (23, 24)
Jelsness-Jorgensen (2012a) (24)	To examine impact of fatigue on disease-related worries in IBD	Cross-sectional study	140 IBD (UC/CD 92/48)	FQ SF-36 IBDQ	-Increased levels of worrying were associated with increased fatigue levels and reduced QoL	Same study as (7, 23)
Jelsness-Jorgensen (2012b) (23)	To investigate occurrence of fatigue among IBS positive IBD individuals in remission	Cross-sectional study	140 (92 UC, 48 CD)	FQ	-Presence of IBS correlated positively with total fatigue scores in UC and CD	High
Kalaitzakis (2008) (8)	Assess potential relation between fatigue and gastrointestinal symptoms in short bowel syndrome	Cross-sectional study	26 SBS (CD/UC 22/2), 41 IBD (CD/UC-13/28), 286 HC	FIS SF-36	- Fatigue has a negative impact on QoL - Fatigue was significantly associated with Anti-TNF/immunomodulator therapy, depression and anxiety. Fatigue was not associated with age, gender and comorbidity	Low
Minderhoud (2003) (10)	To assess the prevalence and severity of fatigue in IBD patients in remission	Cross-sectional study	80 IBD	MFI	- 41% of IBD patients in remission suffered from fatigue	Med
Norton (2015) (11)	To assess 3 fatigue assessment scales in IBD and to determine correlates of fatigue	Cross-sectional study	605 (164 UC, 301 CD)	IBD-F MFI MAF	Univariate analysis - Females, CD patients (IBD-F, MFI), individuals with higher levels of anxiety and depression had significantly higher levels of fatigue. IBDQ total scores were strongly associated with fatigue. Those working part-time and those not working had higher physical fatigue compared to individuals working full time (IBF-F, MFI, MAF) Multivariate analysis - IBD-F: 45% of variability of fatigue was predicted by female gender, depression, CD and poorer QoL. MAF: age, depression and IBDQ score were	High

					all independently associated with fatigue, 48% of fatigue was attributable to these factors. MFI: gender, depression and IBDQ were all independently associated with fatigue, 42% of the variability in general fatigue could be attributed to these factors	
Opheim (2014a) (25)	To examine fatigue interference with daily living in IBD individuals and to explore relationships between severe fatigue interference and socio-demographic and clinical variables as well as CAM use	Cross-sectional study	428 (190 UC, 238 CD)	FSS-5	-Female gender, CD diagnosis and active disease were significantly associated with higher fatigue. Univariate analysis -Female gender, CAM use, active disease, the presence of at least one comorbid condition were significantly associated with fatigue in UC. Disease activity, adverse drug reaction were significantly associated with fatigue in CD. Patients who were working, had a higher education level or income were less likely to report severe interference Multivariate analysis - CAM use and disease activity remained factors independently associated with fatigue in UC. Current smoking and having an active disease remained independently associated with fatigue in CD.	Med Same study as (26)
Opheim (2014b) (26)	To explore associations between socio-demographic, disease-related and personal variables and SOC	Cross-sectional study	428 (190 UC/238 CD)	FSS-5	-Mean FSS-5 score was higher in CD patients compared to UC patients. -In UC, FSS-5 was negatively associated with lower scores on all 3 SOC sub dimensions. In CD, FSS-5 was negatively associated with manageability & meaningfulness	High Same study as (25)
Pellino et al. (2014) (55)	To assess patient-reported fatigue in IBD patients and in controls	Cross-sectional study	16 IBD and 16 Controls	FIS	-Patients with IBD had more severe overall fatigue compared to non-IBD controls. When considering IBD patients with mild to low active disease (n = 11), young IBD patients showed a non-significant trend toward higher fatigue	Med
Piche (2010) (33)	To investigate the prevalence of IBS-like symptoms in CD patients in remission and impact of IBS-like symptoms on fatigue and QoL	Cross-sectional study	92 quiescent CD, 40 IBS and 20 healthy subjects	FIS	- There were significant correlations between the severity of symptoms and QoL, the severity of fatigue, depression, and anxiety in both IBS and CD patients	Med
Romkens (2011) (78)	To assess the prevalence and possible determinants of fatigue in IBD outpatients	Cross-sectional study	117 CD & 55 UC	PFS	-64% reported fatigue regardless of clinical activity; 40% in clinical remission (HBI≤5) reported fatigue -None of the studied determinants of fatigue were significantly correlated with the presence of fatigue	Med
Simren (2008) (34)	Evaluate factors of importance for fatigue in patients with chronic gastrointestinal diseases (IBS & IBD)	Cross-sectional study	223 IBD (UC/CD 133/90), 112 IBS	FIS	- Patients with IBS and IBD were more fatigued than controls - Patients with IBS were more fatigued than patients with IBD - Psychological well-being, sleep disturbances and employment status were independently associated with the severity of fatigue	Med

Tanaka (2005) (51)	Elucidate factors influencing perception of difficulties of life and psychological well-being of patients with UC in remission	Cross-sectional study	72 UC	Questionnaire developed by the authors	- Emotive coping, low social support and high difficulties in life influence the scores for fatigue	Low
Tinsley (2011) (35)	To validate the FACIT-F scale in IBD	Cross-sectional study	209 IBD	FACIT-F	- Disease activity was significantly positively associated with fatigue levels - Fatigue was not significantly associated to CRP. There were no significant differences in fatigue according to disease type	Med
Van Langenberg et al. (2014b) (48)	To measure and compare self-reported fatigue with skeletal muscle fatigue in CD subjects and healthy controls, and to identify associated factors that may be amenable to change	Cross-sectional study	27 consecutive CD patients and 22 matched HC (part of the same sample as (13))	FIS	- The rate of muscle fatigue was significantly greater in the CD patients compared to controls. Maximal force production was not significantly different between the CD and control group - There was a significant negative correlation, between subjective physical fatigue and objectively measured rate of muscle rate of muscle fatigue. Those reporting greater fatigue via survey tended to demonstrate greater muscle fatigue as tested during exercise on the dynamometer	High
Vogelaar et al. (2015) (47)	To assess level of physical fitness and daily physical activity in IBD patients and whether fatigue is associated with impaired physical fitness and impaired physical activity	Cross-sectional study	10 IBD patients with fatigue and 10 without fatigue	CIS-fatigue	- Fatigued patients showed a significantly lower intensity of daily physical activity (motility) and an impaired physical fitness compared with non-fatigued patients - Clinical characteristics such as surgery, disease activity, age at diagnosis, disease type, disease type, body composition, medication use and side effects to medication were not significantly different between fatigued and non-fatigued patients	High
Yoo et al. (2014) (37)	To investigate fatigue level and fatigue-related factors among Korean IBD patients	Cross-sectional study	128 (68 UC/60 CD) + HCs	FACIT-F BFI	-There was no difference in fatigue according to disease type -In FACIT-F and all sub dimensions of BFI except walking ability, both UC and CD patients showed significantly increased fatigue symptoms compared to controls. In CD, ESR and disease activity were significantly correlated with global BFI in the unadjusted regression analysis. But after adjustment none of the factors were statistically significant - Anaemia was a significant determinant of both global BFI and FACIT-F. ESR significantly correlated with FACIT-F	Med

Key: **anti-TNF**- anti-tumour necrosis factor; **BFI** - Brief Fatigue Inventory; **CAM** - complementary and alternative therapies; **CAU** - care as usual; **CD**- Crohn's disease; **CFS** – Chalder Fatigue Scale; **CIS** - Checklist Individual Strength – fatigue; **CRP**- c-reactive protein; **DFIS** - Disease Fatigue Impact Scale; **EQ5D** - Euro Quality of Life; **ESR**- Erythrocyte sedimentation rate; **FACIT-F** - Functional Assessment of Chronic Illness Therapy-Fatigue scale; **FIS** - Fatigue Impact Scale; **FQ** - Fatigue Questionnaire; **FSS** - Fatigue Severity Scale; **FSS-5** - Five-Item Fatigue Severity Scale; **fVAS** - Fatigue visual analogue scale; **GSCL (fatigue)** - Short Form Giessen Subjective Complaints List; **Hb**- haemoglobin; **HRQoL** –Health-related quality of life; **IBD-F** - Inflammatory Bowel Disease- Fatigue; **IBDQ** - Inflammatory Bowel Disease Questionnaire; **IBDU**-inflammatory bowel disease unclassified; **HC** - healthy controls; **MAF** - Multidimensional Assessment of Fatigue; **MFI** - Multidimensional Fatigue Inventory; **MFIS** - Modified Fatigue Impact Scale; **MS**- multiple sclerosis; **PFS** - Piper Fatigue Scale; **PBT** – Problem solving therapy; **PSC**- primary sclerosing cholangitis; **PSHI**- Post Surgical Handicap Index; **PST**- problem solving therapy; **QoL** - quality of life; **SBS**- short bowel syndrome; **SF-36** – Health Survey Short Form-36; **SOC** - sense of coherence; **SFT** - solution-focused therapy; **UC**- ulcerative colitis; **5-ASA**- aminosalicylate

Appendix II: PhD Paper 1 Supplementary Table 2

Potentially modifiable physical factors associated with IBD-fatigue (p values in univariate analysis as reported in published papers).

First author (Year of publication)	Disease activity	ESR	Platelets	CRP	Ferritin deficiency	Low Hb	Corticosteroids	Anti-TNF/ immunomodulators	Exercise	Physical functioning/fitness	Muscle fatigue	Albumin	Omega-3 fish oil	Vitamin B	Smoking	Pain/ Analgesics
Bager (2012)	+ ve 0.05 (HBI >4, SSCAI >4)			N.S.		+ ve 0.05 CD male										
Banovic (2010)	N.S. ≠ (CDAI >150)															
Banovic (2012a)					N.S.			N.S.								
Bjornnsson (2004)	+ ve 0.001 (GSRs)															+ve 0.001
Bol (2010)	+ ve 0.01 (CAI)															
Castillo (2013)	+ ve 0.001 (HBI >3, CAI >6)															
Cohen (2014)	+ ve 0.002* (HBI >5, SSCAI >5)															
Goldenberg (2013)	+ ve 0.001 (HBI ≥5, Powell-Tuck ≥5)				N.S.	N.S.										
Graff (2011)	+ ve 0.001 (HBI ≥5, Powell-Tuck ≥5)			N.S.		N.S.										
Graff (2013)	+ ve 0.001 (HBI ≥5, Powell-Tuck ≥5)			N.S.		N.S.										
Grimstad (2015)	N.S. †(HBI ≥5, MS >2)			N.S.	N.S.	N.S.										
Hauser (2005)	+ ve 0.03 (CAI ≥4)															- ve 0.05
Jelsness - Jorgensen (2010)		+ ve 0.039		+ve 0.027		+ ve 0.012										
Jelsness - Jorgensen (2011)						+ve 0.05	N.S.									
Kalaitzakis (2008)																N.S.

Lichtenstein (2002)										-ve 0.038
Loftus (2008)										-ve 0.0001
Kappelman (2014)	+ ve 0.001 (SCDAI>150, SCCAI ≥4)					+ve 0.001				
Minderhoud (2003)				N.S.						
Minderhoud (2007)										- ve 0.05
Opheim (2014a)	+ ve 0.001 (HBI ≥4, SCCAI >3)				N.S.		N.S.			+ve 0.09**
Piche (2010)	+ ve 0.0005 (CDAI>150) †									
Romberg-Camps (2010)					+ ve 0.05 #					
Simren (2008)	+ ve 0.0001~		N.S.	N.S.		+ ve 0.0001			+ ve 0.01	
Tinsley (2011)	+ ve 0.001 (HBI ≥5, SCCAI ≥5)			N.S.						
Van Langenberg (2014a) **	+ ve 0.001 (HBI, SCCAI)					+ve 0.003	+ve 0.03	-ve 0.001		-ve +ve 0.05
Van Langenberg (2014b) **									+ve 0.05	
Vogelaar (2013)	+ ve 0.001 (HBI ≥5)									
Vogelaar (2015)									+ve 0.037	
Yoo et al. (2014)	+ ve 0.022* (CDAI, MS)	p = .016 #		p = .005#						

Key: **anti-TNF**- tumour necrosis factor; **CAI** – Clinical Activity Index; **CDAI** – Crohn’s Disease Activity Index; **CRP**- C - reactive protein; **ESR**- erythrocyte sedimentation rate; **GSRS**- Gastrointestinal Symptom Rating Scale; **Hb**- haemoglobin; **HBI** – Harvey Bradshaw Index; **MS** – Mayo Score; **N.S.**- non-significant; **SCCAI**- Simple Clinical Colitis Activity Index; **SCDAI** – Short Crohn’s Disease Activity Index; **only for CD individuals; #only for UC individuals, ¥ disease activity measured with calprotectin; † disease activity measured with endoscopic, radiological and/or haematological investigations (*i.e.* Crohn’s Disease Endoscopic Index Score, small bowel enteroclysis, inflammatory markers [haemoglobin, CRP, ESR, platelets and albumin], ~ disease activity measured with haematological investigations (CRP, albumin, haemoglobin and platelets), + ve, positive association at $p < 0.05$; - ve, negative association $p < 0$.

Appendix III: Systematic review search strategy example

EMBASE 1974 to 2015

1. exp Crohn disease/ or crohn*.mp.
2. (colitis and ulcerat*).mp. or exp ulcerative colitis/
3. (inflammatory bowel disease* or IBD).mp.
4. 1 or 2 or 3
5. exp fatigue/
6. (energy OR tired* OR sleep* OR drows* OR letharg* OR exhaust*).mp.
7. (lack OR loss OR lost) adj (energy OR vigo* OR vitality).mp.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to (human and english language and yr="2012 -Current" and (adult <18 to 64 years> or aged <65+ years>))

Appendix IV: PhD Paper 2 Supplementary Table 1

Supplementary Table 1: Univariate correlations between fatigue, QoL and sociodemographic, clinical and psychosocial predictor variables ($n = 182$).

	IBD-F1	IBD-F2	MFI *	# IBDQ
Sociodemographic and clinical				
Age	-.01	-.07	-.04	.03
Albumin	.05	-.02	-.15	.01
CRP	-.16	-.05	.02	.03
Disease activity	.41	.48	.30	-.61
Faecal calprotectin ($n = 61$)	.28	.18	.02	-.47
Ferritin ($n = 107$)	.07	.04	.10	-.02
Folate ($n = 85$)	-.04	-.10	.08	.05
Haemoglobin	-.05	-.06	-.09	.11
Platelets	.13	.12	.14	-.15
Vitamin B12 ($n = 105$)	.17	.15	.13	-.11
Years since diagnosis	-.02	-.01	.04	.10
Emotional				
HADS anxiety	.47	.53	.46	-.50
HADS depression	.52	.69	.52	-.57
IBD-D distress	.56	.71	.53	-.72
PSS stress	.37	.48	.50	-.42
Cognitive				
BIPQ fatigue perceptions	.63	.56	.51	-.39
Catastrophising	.44	.52	.41	-.51
Damage beliefs	.30	.34	.29	-.39
Embarrassment avoidance	.39	.53	.48	-.50
Fear avoidance	.33	.47	.47	-.42
Symptom focus	.41	.48	.41	-.44
Behavioural				
All-or-nothing behaviour	.48	.62	.43	-.54
Avoidance behaviour	.47	.70	.51	-.55
ESS daytime sleepiness	.49	.54	.44	-.38
IBDQ QoL	-.62	-.73	-.51	

Figures in bold are Pearson r correlations statistically significant: $p < 0.10$; # The IBDQ total score is made up from the individual subscales; IBD-F1 Fatigue severity; IBD-F2 Fatigue impact on daily activities; *MFI General Fatigue subscale. Data presented for $n = 182$ unless specified in parentheses.

Key: Anti-TNF- anti-tumour necrosis factor; BIPQ – Brief Illness Perceptions Questionnaire; CRP- C-reactive protein; ESS – Epworth Sleepiness Scale; HADS – Hospital Anxiety and Depression Scale; IBD-D – Inflammatory Bowel Disease Distress Scale; IBD-F –

Inflammatory Bowel Disease-Fatigue Scale; IBDQ- Inflammatory Bowel Disease Questionnaire; MFI- Multidimensional Fatigue Inventory; PSS – Cohen Perceived Stress Scale; QoL – quality of life.

Appendix V: PhD Paper 2 Supplementary Table 2

Supplementary Table 2: Univariate Independent samples T-tests of differences between fatigue and QoL according to sociodemographic and clinical predictor variables ($n = 182$).

	IBD-F1		IBD-F2		MFI *		M _D	IBDQ #
	MD	90% CI	MD	90% CI	MD	90% CI		90% CI
Sociodemographic								
Female gender	2.90	1.77, 4.03	11.29	4.73, 17.84	2.02	1.07, 2.98	-5.88	-9.41, -2.36
Clinical								
5-ASA	-0.53	-1.75, 0.17	-8.60	-15.44, -1.76	-0.69	-1.71, 0.33	1.49	-2.22, 5.20
Antibiotics	1.41	-2.16, 4.99	2.18	-18.10, 22.45	1.53	-1.42, 4.50	-6.61	-17.47, 4.24
Anti-TNF	0.94	0.30, 2.17	8.73	1.85, 15.62	1.28	0.27, 2.30	-2.22	-5.98, 1.51
Current stoma	5.32	2.70, 7.95	33.24	18.51, 47.98	3.82	1.21, 6.42	-12.04	-20.12, -3.97
Exercise <30 mins ~	1.77	0.55, 2.99	9.07	2.15, 15.98	2.37	1.39, 3.35	-4.39	-9.86, 0.07
Methotrexate	2.22	-1.76, 6.20	19.29	-3.19, 41.77	3.62	0.35, 6.89	-13.98	-26.00, -1.96
Previous surgery	0.97	-0.26, 2.20	6.30	-0.59, 13.20	0.45	-0.57, 1.47	-3.33	-7.03, 0.38
Steroids	1.54	-0.52, 3.60	17.90	6.40, 29.40	1.35	-0.35, 3.05	-13.76	-19.81, -7.70
Thiopurines	-1.29	-2.26, -0.12	-5.86	-12.48, 0.75	-0.69	-1.66, 0.29	5.02	0.83, 9.22
Vedolizumab	-0.26	-3.31, 2.78	5.43	-11.79, 22.66	-1.04	-3.55, 1.48	-4.25	-13.49, 4.99

Figures in bold are independent samples T tests statistically significant $p < 0.10$; # The IBDQ total score is made up from the individual subscales; IBD-F1 Fatigue severity; IBD-F2 Fatigue impact on daily activities; * MFI General Fatigue subscale; ~ < 30 minutes of aerobic exercise per week.

Key: anti-TNF – anti-tumour necrosis factor; CI – confidence intervals; IBD-F – Inflammatory Bowel Disease-Fatigue Scale; IBDQ- Inflammatory Bowel Disease Questionnaire; MD- mean difference; MFI- Multidimensional Fatigue Inventory; 5-ASA – aminosalicylates.

Appendix VI: PhD Paper 2 Supplementary Table 3

Supplementary Table 3: Univariate one-way between groups ANOVAs of differences between fatigue and QoL according to sociodemographic and clinical predictor variables ($n = 182$).

	IBD-F1	IBD-F2	MFI*	IBDQ*
Sociodemographic				
Education status	$F(2, 176) = 4.91, p = 0.01$	$F(2, 177) = 3.41, p = 0.03$	$F(2, 174) = 1.04, p = 0.36$	$F(2, 177) = 4.92, p = 0.01$
Employment	$F(4, 171) = 4.70, p = 0.01$	$F(4, 172) = 8.06, p = 0.01$	$F(4, 170) = 2.46, p = 0.05$	$F(4, 172) = 4.22, p = 0.01$
Living status	$F(5, 169) = 1.29, p = 0.27$	$F(5, 170) = 1.55, p = 0.18$	$F(5, 168) = 0.30, p = 0.91$	$F(5, 170) = 3.63, p = 0.01$
Marital status	$F(5, 169) = 2.49, p = 0.03$	$F(5, 170) = 1.73, p = 0.13$	$F(5, 168) = 1.73, p = 0.13$	$F(5, 170) = 2.18, p = 0.08$
Clinical				
Diagnosis	$F(2, 178) = 1.66, p = 0.19$	$F(2, 178) = 1.66, p = 0.19$	$F(2, 176) = 5.22, p = 0.01$	$F(2, 179) = 1.61, p = 0.20$
Smoking status	$F(2, 177) = 2.78, p = 0.06$	$F(2, 178) = 1.66, p = 0.19$	$F(2, 175) = 1.26, p = 0.29$	$F(2, 178) = 3.96, p = 0.02$

Figures in bold are independent samples T tests statistically significant $p < 0.10$. # The IBDQ total score is made up from the individual subscales, IBD-F1 Fatigue severity, IBD-F2 Fatigue impact on daily activities, * MFI General Fatigue subscale

Key: IBD-F – Inflammatory Bowel Disease-Fatigue Scale; IBDQ- Inflammatory Bowel Disease Questionnaire; MFI- Multidimensional Fatigue Inventory.

Appendix VII: Cross-sectional study Patient Information Sheet

Study Title: Evaluating fatigue in inflammatory bowel disease

Version 1.6 Date: 03-07-2015

Chief Investigator: Professor Christine Norton, Professor of Nursing, King's College London

Principle Investigator: Julie Duncan, IBD Clinical Nurse Specialist, Guy's & St Thomas' Hospitals

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with family, friends or your care team if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Fatigue is one of the most common symptoms in patients with IBD and it can impact on patients' quality of life. This study aims to explore levels of fatigue in IBD patients to understand how fatigue symptoms change over time. Several factors are likely to explain fatigue levels. These include psychological factors such as people's beliefs about their fatigue levels. Increasing our knowledge of the relationship between fatigue and psychological factors may lead to better ways to help patients cope with fatigue and its consequences. The study is part of a student project and it will form part of a PhD developing an intervention for fatigue in patients with IBD.

Why I have been chosen?

You have been given this leaflet because you have IBD. You do not have to live in London to take part, and you do not have to experience fatigue. We need a mixture of both people who are fatigued and non-fatigued people, so that we can understand fatigue better.

Do I have to take part?

No. It is up to you to decide whether or not you take part. You may wish to discuss your decision with your close family, friends and with your IBD nurse specialist. If you do decide to take part, you will be asked to sign a consent form. You will still be free to withdraw at any time and without the need to give a reason. If you decide to withdraw, the data collected from you up until that time will be used in the analysis of the results, unless you specify not to do so. You will not be able to withdraw your data from the study after the analysis of the data has been conducted. If you decide not to take part, or later decide to withdraw, it will not affect the care you receive.

What will happen if I take part?

If after reading this information sheet, you think that you are interested in the study, you will be given questionnaires and a consent form to take home. The questionnaires measure fatigue symptoms, sleep problems, stress, mood, beliefs about fatigue and its impacts upon your life. The questionnaires take about 30 to 60 minutes to complete. You can take time to consider your participation in the study and discuss your decision with family, friends and care team. We will provide you with a pre-paid reply envelope so you can send a signed consent form and the completed questionnaires back to us.

If you decide to take part you will be involved in the study for a period of 2 years. You will be asked to complete the questionnaires within 7 days of receiving the first questionnaire pack and again in 12 and 24 months. You will receive each set of questionnaires on separate occasions. There will also be an option to complete the questionnaires at each time point via the internet if you prefer this to posting them back to us. We will ask you for your contact information so that we can send you follow-up questionnaires via post or email. We will collect some results from your records of any routine blood tests that you have had close to each of the study-time points. We will not ask for any additional blood tests, but we do need your permission to access your medical notes so we can record these results.

When you have completed all questionnaires three times and sent them back to us, you will not have to do anything else for this study.

What are the possible disadvantages and risks of taking part?

We believe there are no disadvantages to taking part in this study, other than the 30 to 60 minutes of your time to complete the questionnaires. If for any reason you feel uncomfortable about any of the questions asked you are reminded of your right to withdraw at any time. If you wish to talk to your doctor or IBD nurse specialist, arrangements can be made.

What are the possible benefits of taking part?

The study will be of no benefit to you but the information we get may help to develop an intervention for fatigue in patients with IBD. If you ask us for it, you will receive a summary report of the findings, when the study is completed in two years' time.

What happens when the research study stops?

After the study stops you are welcome to a summary of the research findings. Personnel from the trust's Research and Development department may require certain information for audit purposes. No individual data or results will be passed on.

Expenses and payments

You will not be paid for taking part in this study. There should be no extra cost to you. Questionnaires will be given or sent to you with a prepaid reply envelope or you can reply via email.

Frequently asked questions

Will my taking part in this study be kept confidential?

Yes. All information collected about you during the study will be kept strictly confidential. Data will be stored securely and handled according to data protection guidelines. Any information about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

It is intended to publish the results of the research study in an appropriate medical journal. No patient will be individually identified in any report or publication. The results will be used to help us develop a treatment for IBD fatigue.

What will happen if I don't want to carry on with the study?

A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you decide to withdraw after the start of the study,

you may do so assured that your data will be kept confidential.
Following withdrawal from the study, your data may still be used
up to that point.

Will my GP be involved?

Your personal GP will not be involved in the study, but they will be informed of your participation with your permission.

What if there is a problem?

If you have any complaint about the way you have been dealt with during the study or concerns about the study please contact the research team which will do their best to answer your questions. Please contact: Professor Christine Norton by email: christine.norton@kcl.ac.uk or telephone: +44 (0) 20 7848 3681.

If you have a complaint, you should talk to a member of the research team who will do their best to answer your questions. If you remain unhappy, you may be able to make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188. Address: PALS, KIC, Ground floor, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH.

This study is sponsored by King's College London. The sponsor will at all times maintain adequate insurance in relation to the study independently.

Contact details

Any questions about the study should be directed to either the Chief or Principal Investigator:

Chief investigator

Professor Christine Norton
Professor of Nursing
Rm 2.24 James Clerk Maxwell Building
57 Waterloo Road
London SE1 8WA
Tel: +44 (0) 20 7848 3681
Email: christine.norton@kcl.ac.uk

Principle investigator

Julie Duncan
IBD Clinical Nurse Specialist
Guy's & St Thomas' Hospital
Great Maze Pond
London, SE1 9RT
Tel: 0207 1882493
Email: Julie.Duncan@gstt.nhs.uk

Please keep this information sheet for your own records.

Appendix VIII: Cross-sectional study Patient Consent Form

Study Title: Evaluating fatigue in inflammatory bowel disease

Version 1.2. Date: 30-04-2015

Chief Investigator: Professor Christine Norton, King's College London

Principle Investigator: Julie Duncan, IBD Clinical Nurse Specialist, Guy's & St Thomas' Hospitals

- | | Please
initial
below |
|--|-------------------------------------|
| 1. I confirm that I have read and understand the Patient information sheet dated 03-07-2015 (Version 1.6) and that I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. | <input type="checkbox"/> |
| 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. | <input type="checkbox"/> |
| 3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals from the research team at King's College London, who will collect information concerning my health. I give permission for these individuals to have access to my data. | <input type="checkbox"/> |
| 4. I understand that I will be asked to complete a set of questionnaires once and will be asked to complete them again another two times (in 12 and 24 months' time) and I agree to do this. | <input type="checkbox"/> |
| 5. I understand I will be asked once to provide some personal, clinical and contact information about myself. | <input type="checkbox"/> |
| 6. I understand that even if I withdraw from the above study, the data collected from me up until that time will be used in analysing the results, unless I specify not to do so. I understand that I will not be able to withdraw data from the study after the analysis of the data. | <input type="checkbox"/> |
| 7. I agree to my GP being informed of my participation in the study. | <input type="checkbox"/> |
| 8. I agree to take part in the above study. | <input type="checkbox"/> |

..... Study Number Today's Date Patient Signature
-----------------------	-----------------------	-----------------------------------

..... PRINTED Name of Researcher Today's Date Signature
-------------------------------------	-----------------------	--------------------

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes

Appendix IX: London Bridge Committee ethical approval letter for cross-sectional study



Telephone: 020 7972 2582

22 July 2015

Professor Christine Norton
Professor of Nursing
King's College London
Florence Nightingale School of Nursing and Midwifery
King's College London
57 Waterloo Road
London SE1 8WA

Dear Professor Norton

Study title: Evaluating fatigue in inflammatory bowel disease patients
REC reference: 15/LO/1081
Protocol number: 1.1
IRAS project ID: 180209

Thank you for your letter of 03 July 2015. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 03 July 2015.

Documents received

The documents received were as follows:

Document	Version	Date
Participant information sheet (PIS) [GSTT]	1.6	03 July 2015
Participant information sheet (PIS) [St Marks]	1.6	03 July 2015

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
Covering letter on headed paper [Cover Letter]	1	27 May 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional Indemnity policy schedule]	1	01 August 2014
GP/consultant information sheets or letters [GP letter Guy's & St Thomas]	1.1	30 April 2015

A Research Ethics Committee established by the Health Research Authority

St Thomas' Hospitals]		
GP/consultant information sheets or letters [GP letter St Mark's Hospital]	1.1	30 April 2015
Letter from sponsor [Email from sponsor]	1	27 May 2015
Non-validated questionnaire [Inflammatory Bowel Disease Distress Scale]	2.1	04 March 2015
Non-validated questionnaire [Clinical details form]	1	28 May 2015
Non-validated questionnaire [Demographic and Clinical Details Form]	1	28 May 2015
Participant consent form [Participant consent form Guy's & St Thomas' Hospitals]	1.2	30 April 2015
Participant consent form [Participant consent form St Mark's Hospital]	1.2	30 April 2015
Participant information sheet (PIS) [GSTT]	1.6	03 July 2015
Participant information sheet (PIS) [St Marks]	1.6	03 July 2015
REC Application Form [REC_Form_29052015]		29 May 2015
Research protocol or project proposal [Research Protocol]	1.1	21 May 2015
Summary CV for Chief Investigator (CI) [Christine Norton_CurriculumVitae]	1	10 April 2015
Summary CV for student [Micol Artom_CurriculumVitae]	1	28 May 2015
Summary CV for supervisor (student research) [Christine Norton_CurriculumVitae]	1	10 April 2015
Summary CV for supervisor (student research) [Professor J Sturt]	April 2015	
Summary CV for supervisor (student research) [Professor Rona Moss-Morris]		06 March 2015
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Summary of protocol]	1	28 May 2015
Validated questionnaire [Belief Illness Perception Questionnaire]	1	28 May 2015
Validated questionnaire [Beliefs about Symptoms Questionnaire]	1	28 May 2015
Validated questionnaire [Hospital Depression and Anxiety Scale]	1	28 May 2015
Validated questionnaire [Epworth Sleepiness Scale]	1	28 May 2015
Validated questionnaire [Perceived Stress Scale]	1	28 May 2015
Validated questionnaire [UK Inflammatory Bowel Disease Questionnaire]	1	28 May 2015
Validated questionnaire [Work Productivity and Activity Impairment Questionnaire]	1	28 May 2015
Validated questionnaire [Multidimensional fatigue inventory]	1	28 May 2015
Validated questionnaire [IBD-Fatigue Scale]	1	30 August 2013
Validated questionnaire [Simple Index of Crohn's Disease Activity and Simple Clinical Colitis Activity Index]	1	28 May 2015

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

15/LO/1081

Please quote this number on all correspondence

Yours sincerely



Stephanie Hill
REC Manager

E-mail: nrescommittee.london-londonbridge@nhs.net

Copy to: *Mr Keith Brennan*
Jennifer Boston, Guys and St Thomas' NHS Foundation Trust

Appendix X: Cross-sectional study questionnaires

Study Number: _____ **Date (DD/MM/YY):** _____

Thank you for agreeing to take part. Please complete the consent form and return all the questionnaires within 7 days from receipt.

Demographic and Clinical Details Form

- | | | |
|-----------|--------|---|
| 1. Gender | Male | 1 |
| | Female | 2 |

2. Age (Years) _____

3. When did your symptoms start?

Month _____

Year _____

4. Which medications are you currently taking for your inflammatory bowel disease?
Please list them below

[illegible]

5. What is the highest level of education you have completed? *Please circle one answer only*

- | | |
|----------------------------------|---|
| School up to age 16 years | 1 |
| School or college up to 18 years | 2 |
| Higher Education | 3 |

6. Do you exercise regularly? Please circle one answer only

- | | |
|---|---|
| More than 30 minutes of aerobic exercise per week | 1 |
| Less than 30 minutes of aerobic exercise per week | 2 |

7. Do you smoke? Please circle one answer only

- Yes 1
- Ex-smoker 2
- No 3

Study Number: _____ **Date (DD/MM/YY):** _____

8. Are you currently? *Please circle one answer only*

- | | |
|-----------------------------|---|
| Married/Living with partner | 1 |
| Widowed | 2 |
| Divorced/Separated | 3 |
| Single parent | 4 |
| Single | 5 |
| Other (_____) | 6 |

9. During the past month were you? *Please circle one answer only*

- | | |
|-------------------------|---|
| Working Full time | 1 |
| Working Part time | 2 |
| Retired | 3 |
| Full time house keeping | 4 |
| Not working | 5 |

10. What members of family live with you? *Please circle one answer only*

- | | |
|---------------------------------------|---|
| Live alone | 1 |
| Live with spouse/partner | 2 |
| Live with spouse/partner and children | 3 |
| Single parent with children | 4 |
| Live with other relatives | 5 |
| Live with friends | 6 |

11. How would you prefer to be reminded about you participation to the study follow-up in 12 and 24 months' time? *Please circle one answer only*

- | | |
|-------------|---|
| Email | 1 |
| Text | 2 |
| Phone | 3 |
| Postal mail | 4 |

12. How would you prefer to receive and return the study follow-up questionnaires in 12 and 24 months' time? *Please circle one answer only*

- | | |
|-------------|---|
| Email | 1 |
| Postal mail | 2 |

If you would like to receive the follow-up questionnaires by email, please complete below

E-mail

13. Would you like to be informed about the results of the study?

- | | |
|-----|---|
| Yes | 1 |
| No | 2 |

Inflammatory Bowel Disease-Fatigue (IBD-F)

SECTION I - Fatigue Assessment Scale

This section of the questionnaire will identify fatigue, its severity, frequency and duration.

Sometimes people with inflammatory bowel disease feel fatigued. The term 'fatigue' is used throughout the questionnaire. Fatigue has been defined as a sense of continuing tiredness, with periods of sudden and overwhelming lack of energy or feeling of exhaustion that is not relieved following rest or sleep.

Please tick ONE number for each question	Score from 0 - 4 with			
	0 = no fatigue		Severe fatigue = 4	
1. What is your fatigue level right NOW	0	1	2	3 4
2. What was your HIGHEST fatigue level in the past two weeks	0	1	2	3 4
3. What was your LOWEST fatigue level in the past two weeks	0	1	2	3 4
4. What was your AVERAGE fatigue level in the past two weeks	0	1	2	3 4
5. How much of your waking time have you felt fatigued in the past two weeks	0 None of the time	1 Some of the time	2 Often	3 Most of the time 4 All the time

SECTION II – IBD-Fatigue Impact on Daily Activities Scale

This section assesses the perceived impact of fatigue on your daily activities in the **past two weeks**.

Please answer all the questions. The possible answers to the questions are: None of the time - 0; Some of the time – 1; Often - 2; Most of the time - 3; All of the time - 4.
If a particular activity does not apply to you, for example you do not drive, please select N/A.

Please tick only ONE answer for each question reflecting on the past two weeks	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
1. I had to nap during the day because of fatigue	0	1	2	3	4	
2. Fatigue stopped me from going out to social events	0	1	2	3	4	
3. I was not able to go to work or college because of fatigue	0	1	2	3	4	N/A
4. My performance at work or education was affected by fatigue	0	1	2	3	4	N/A
5. I had problems concentrating because of fatigue	0	1	2	3	4	
6. I had difficulty motivating myself because of fatigue	0	1	2	3	4	
7. I could not wash and dress myself because of fatigue	0	1	2	3	4	
8. I had difficulty with walking because of fatigue	0	1	2	3	4	
9. I was unable to drive as much as I need to because of fatigue	0	1	2	3	4	N/A
10. I was not able to do as much physical exercise as I wanted to because of fatigue	0	1	2	3	4	

Please tick only ONE answer for each question reflecting on the past two weeks						
	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
11. I had difficulty continuing with my hobbies/interests because of fatigue	0	1	2	3	4	
12. My emotional relationship with my partner was affected by fatigue	0	1	2	3	4	N/A
13. My sexual relationship with my partner was affected by fatigue	0	1	2	3	4	N/A
14. My relationship with my children was affected by fatigue	0	1	2	3	4	N/A
15. I was low in mood because of fatigue	0	1	2	3	4	
16. I felt isolated because of fatigue	0	1	2	3	4	
17. My memory was affected because of fatigue	0	1	2	3	4	
18. I made mistakes because of fatigue	0	1	2	3	4	
19. Fatigue made me irritable	0	1	2	3	4	
20. Fatigue made me frustrated	0	1	2	3	4	
21. I got words mixed up because of fatigue	0	1	2	3	4	
22. Fatigue stopped me from enjoying life	0	1	2	3	4	
23. Fatigue stopped me from having a fulfilling life	0	1	2	3	4	
24. My self-esteem was affected by fatigue	0	1	2	3	4	
25. Fatigue affected my confidence	0	1	2	3	4	

Please tick only ONE answer for each question reflecting on the past two weeks					
	None of the time	Some of the time	Often	Most of the time	Not applicable
26. Fatigue made me feel unhappy	0	1	2	3	4
27. I had difficulties sleeping at night because of fatigue	0	1	2	3	4
28. Fatigue affected my ability to do all my normal household activities	0	1	2	3	4
29. I had to ask others for help because of fatigue	0	1	2	3	4
30. Quality of my life was affected by fatigue	0	1	2	3	4

SECTION III – Additional Questions about your Fatigue

1. What do you think is the main cause of your fatigue apart from IBD?
.....
.....
2. What do you think are the other causes of your fatigue?
.....
.....
3. Have you found anything that helps with your fatigue?
.....
.....
4. How long have you experienced fatigue? years months
5. During this time has your fatigue been: a) Constant b) Intermittent

IBD-Fatigue Scale: FINAL.30.08.2013

Multidimensional Fatigue Inventory (MFI)

The next questions are about how you have been feeling lately. Please place one "X" for each statement.

The more you agree with the statement, the more you should place an "X" in the direction of "yes, that is true." The more you disagree with the statement, the more you should place an X in the direction of "no, that is not true."

Take for example the statement: "I FEEL RELAXED."

If you think that this statement is entirely true, that you have been feeling relaxed lately, you would place an "X" in the box labeled "1."

yes, that is true ☒ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

1. I feel fit. yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

2. Physically I feel only able to do a little. yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

3. I feel very active. yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

4. I feel like doing all sorts of nice things. yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

5. I feel tired. yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

6. I think I do a lot in a day. yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

©E.Smets, B.Garssen, B.Bonke

7. When I am doing something, I can keep my thoughts on it.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

8. Physically I can take on a lot.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

9. I dread having to do things.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

10. I think I do very little in a day.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

11. I can concentrate well.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

12. I am rested.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

13. It takes a lot of effort to concentrate on things.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

14. Physically I feel I am in a bad condition.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

15. I have a lot of plans.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

16. I tire easily.

yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

17. I get little done.

yes, that is true

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5

no, that is not true

18. I don't feel like doing anything.

yes, that is true

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5

no, that is not true

19. My thoughts easily wander.

yes, that is true

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5

no, that is not true

20. Physically I feel I am in an excellent condition.

yes, that is true

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5

no, that is not true

The UK Inflammatory Bowel Disease Questionnaire (IBDQ)

The following questions ask about your bowel problem and how it affected your life over the last two weeks. Please tick one answer for each of the questions. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

1. On how many days over the last two weeks have you had loose or runny bowel movements?

a) None	<input type="checkbox"/>
b) On one or two days only	<input type="checkbox"/>
c) On three to seven days	<input type="checkbox"/>
d) On eight to fourteen days (i.e. more than every other day)	<input type="checkbox"/>

2. On how many days over the last two weeks have you felt tired?

a) None	<input type="checkbox"/>
b) On one or two days only	<input type="checkbox"/>
c) On three to seven days	<input type="checkbox"/>
d) On eight to fourteen days (i.e. more than every other day)	<input type="checkbox"/>

3. In the last two weeks have you felt frustrated?

a) No, not at all	<input type="checkbox"/>
b) Yes, some of the time	<input type="checkbox"/>
c) Yes, most of the time	<input type="checkbox"/>
d) Yes, all of the time	<input type="checkbox"/>

4. In the last two weeks, has your bowel condition prevented you from carrying out your work or other normal activities?

a) No, not at all	<input type="checkbox"/>
b) Yes, for one or two days	<input type="checkbox"/>
c) Yes, for three to seven days	<input type="checkbox"/>
d) Yes, for eight to fourteen days (i.e. more than every other day)	<input type="checkbox"/>

5. On how many days over the last two weeks have you opened your bowels more than three times a day?

a) None	<input type="checkbox"/>
b) On one or two days only	<input type="checkbox"/>
c) On three to seven days	<input type="checkbox"/>
d) On eight to fourteen days (i.e. more than every other day)	<input type="checkbox"/>

6. On how many days over the last two weeks have you felt full of energy?

a) None	<input type="checkbox"/>
b) On one to two days only	<input type="checkbox"/>
c) On three to seven days	<input type="checkbox"/>
d) On eight to fourteen days (ie more than every other day)	<input type="checkbox"/>

7. In the last two weeks have you been worried about being admitted to hospital because of your bowel problem?

- a) No, not at all ☐
- b) Yes, some of the time ☐
- c) Yes, most of the time ☐
- d) Yes, all of the time ☐

8. In the last two weeks did your bowel condition prevent you from going out socially?

- a) No, not at all ☐
- b) Yes, some of the time ☐
- c) Yes, most of the time ☐
- d) Yes, all the time ☐
- e) Does not apply to me ☐

9. On how many days over the last two weeks have your bowels opened accidentally?

- a) None ☐
- b) On one or two days only ☐
- c) On three to seven days ☐
- d) On eight to fourteen days (ie more than every other day) ☐

10. On how many days over the last two weeks have you felt generally unwell?

- a) None ☐
- b) On one or two days only ☐
- c) On three to seven days ☐
- d) On eight to fourteen days (i.e. more than every other day) ☐

11. In the last two weeks have you felt the need to keep close to a toilet?

- a) No, not at all ☐
- b) Yes, some of the time ☐
- c) Yes, most of the time ☐
- d) Yes, all of the time ☐

12. In the last two weeks, has your bowel condition affected your leisure or sports activities?

- a) No, not at all ☐
- b) Yes, some of the time ☐
- c) Yes, most of the time ☐
- d) Yes, all of the time ☐
- e) Does not apply to me ☐

13. On how many days over the last two weeks have you felt pain in your abdomen?

- a) None ☐
- b) On one or two days only ☐
- c) On three to seven days ☐
- d) On eight to fourteen days (i.e. more than every other day) ☐

14. On how many nights over the last two weeks have you been unable to sleep well (days if you are a shift worker)?

- a) None []
- b) On one or two nights only []
- c) On three to seven nights []
- d) On eight to fourteen nights (i.e. more than every other night) []

15. In the last two weeks have you felt depressed?

- a) No, not at all []
- b) Yes, some of the time []
- c) Yes, most of the time []
- d) Yes, all of the time []

16. In the last two weeks have you had to avoid attending events where there was no toilet close at hand?

- a) No, not at all []
- b) Yes, some of the time []
- c) Yes, most of the time []
- d) Yes, all of the time []

17. On how many days over the last two weeks, have you had a problem with large amounts of wind?

- a) None []
- b) On one or two days only []
- c) On three to seven days []
- d) On eight to fourteen days (i.e. more than every other day) []

18. On how many days over the last two weeks have you felt off your food?

- a) None []
- b) On one or two days only []
- c) On three to seven days []
- d) On eight to fourteen days (ie more than every other day) []

19. Many patients with bowel problems have worries about their illness. How often during the last two weeks have you felt worried?

- a) No, not at all []
- b) Yes, some of the time []
- c) Yes, most of the time []
- d) Yes, all of the time []

20. On how many days over the last two weeks has your abdomen felt bloated?

- a) None []
- b) On one or two days only []
- c) On three to seven days []
- d) On eight to fourteen days (i.e. more than every other day) []

21. In the last two weeks have you felt relaxed?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []
22. On how many days over the last two weeks have you noticed blood with your bowel movements?
- a) None []
 - b) On one or two days only []
 - c) On three to seven days []
 - d) On eight to fourteen days (ie more than every other day) []
23. In the last two weeks have you been embarrassed by your bowel problem?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []
24. On how many days over the last two weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?
- a) None []
 - b) On one or two days only []
 - c) On three to seven days []
 - d) On eight to fourteen days (i.e. more than every other day) []
25. In the last two weeks have you felt upset?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []
26. On how many days over the last two weeks have you had to rush to the toilet?
- a) None []
 - b) On one or two days only []
 - c) On three to seven days []
 - d) On eight to fourteen days (i.e. more than every other day) []
27. In the last two weeks have you felt angry as a result of your bowel problem?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []

28. In the last two weeks, has your sex life been affected by your bowel problem?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []
 - e) Does not apply to me []
29. On how many days over the last two weeks have you felt sick?
- a) None []
 - b) On one or two days only []
 - c) On three to seven days []
 - d) On eight to fourteen days (i.e. more than every other day) []
30. In the last two weeks have you felt irritable?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []
31. In the last two weeks have you felt lack of sympathy from others?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []
32. In the last two weeks have you felt happy?
- a) No, not at all []
 - b) Yes, some of the time []
 - c) Yes, most of the time []
 - d) Yes, all of the time []

Belief Illness Perception Questionnaire (B-IPQ)

For the following questions, please mark a number that best corresponds to your views:

a. How much do fatigue symptoms affect you currently?

[illegible]

b. How long do you think your fatigue symptoms will continue?

A very short 0 1 2 3 4 5 6 7 8 9 10 Forever
time

c. How much control do you feel you have over your fatigue?

Absolutely 0 1 2 3 4 5 6 7 8 9 10 Extreme amount
no control of control

d. How much do you think your treatment can help your fatigue symptoms?

Not at all 0 1 2 3 4 5 6 7 8 9 10 Extremely helpful

e. How concerned are you about your fatigue symptoms?

Not at all 0 1 2 3 4 5 6 7 8 9 10 Extremely
concerned concerned

f. How well do you feel you understand your fatigue symptoms?

[illegible]

g. How much does your fatigue symptoms affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

Not at all emotionally 0 1 2 3 4 5 6 7 8 9 10 Extremely affected at all emotionally

Beliefs about Symptoms Questionnaire (CBSQ)

We are very interested in finding out more about the symptoms of your **fatigue** and the impact these symptoms have had on your life. There are no **right** or **wrong** answers to these questions. We are most interested in your **own** personal views rather than those of your family or the people who are treating you.

Please indicate how much you agree or disagree with the following statements about your current symptoms by ticking the appropriate box.

	VIEWS ABOUT YOUR <u>FATIGUE</u> SYMPTOMS	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
FA1	I am afraid that I will make my symptoms worse if I exercise					
FA2	My symptoms would be relieved if I were to exercise					
FA3	Avoiding unnecessary activities is the safest thing I can do to prevent my symptoms from worsening					
FA4	The severity of my symptoms must mean there is something serious going on in my body					
FA9	Even though I experience symptoms, I don't think they are actually harming me					
FA10	When I experience symptoms, my body is telling me that there is something seriously wrong.					
FA12	Physical activity makes my symptoms worse					
FA14	Doing less helps symptoms					
FA15	Symptoms are a signal that I am damaging myself					
FA16	I am afraid I will have more symptoms if I am not careful					
FA17	I should avoid exercise when I have symptoms					
C1	I worry that I may become permanently bedridden because of my symptoms					
C2	I think that if my symptoms get too severe they may never decrease					
C4	My illness is awful and I feel that it overwhelms me					
C6	I will never feel right again					

	VIEWS ABOUT YOUR <u>FATIGUE</u> SYMPTOMS	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
<i>SF1</i>	When I experience symptoms, I think about them constantly					
<i>SF2</i>	I worry when I am experiencing symptoms					
<i>SF3</i>	When I am experiencing symptoms it is difficult for me to think of anything else					
<i>SF5</i>	I think a great deal about my symptoms					
<i>SF9</i>	My symptoms are always at the back of my mind					
<i>SF12</i>	I spend a lot of time thinking about my illness					
<i>EA1</i>	I am embarrassed about my symptoms					
<i>EA2</i>	I worry that people will think badly of me because of my symptoms					
<i>EA3</i>	The embarrassing nature of my symptoms prevents me from doing things					
<i>EA4</i>	I avoid social situations because I am scared my symptoms will get out of control					
<i>EA5</i>	I am ashamed of my symptoms					
<i>EA6</i>	My symptoms have the potential to make me look foolish in front of other people					

We are interested in how you respond to or manage your **fatigue** symptoms at the moment. Listed below are a number of different responses that people may have to their symptoms.

Please indicate how often you respond in the following ways by ticking the appropriate box. Choose the most accurate answer for YOU, not what you think "most people" would say or do.

	MANAGING FATIGUE SYMPTOMS	Never	Some-times	Quite often	Very Often	All the time
L2	I stay in bed to control my symptoms					
L3	When I experience symptoms, I rest.					
L4	I tend to avoid activities that make my symptoms worse					
L7	I tend to nap during the day to control my symptoms					
AL1	I tend to overdo things when I feel energetic					
AL2	I find myself rushing to get things done before I crash					
AL3	I tend to overdo things and then rest up for a while					
AL4	I tend to do a lot on a good day and rest on a bad day					
L9	I sleep when I'm tired in order to control my symptoms					
L10	I avoid making social arrangements in case I'm not up to it.					
L11	I avoid exerting myself in order to control my symptoms					
AL5	I'm a bit all or nothing when it comes to doing things					
L13	I avoid stressful situations					

Which of the following best describes the nature of your **fatigue symptoms (please tick one):**

My symptoms are physical	My symptoms are mainly physical	Both physical and psychological factors are involved in my symptoms	My symptoms are mainly psychological	My symptoms are psychological in nature

Disease Activity Index (DAI)

Please complete whichever of the following disease activity indexes are relevant to you. If you have Crohn's Colitis, please complete both scores. You should score these according to how your Crohn's or Ulcerative Colitis is **on the day** you complete the index. If you have proctitis, please complete the UC score.

SIMPLE INDEX OF CROHN'S DISEASE ACTIVITY (Harvey & Bradshaw 1980)

A. General wellbeing <i>Please select one</i> <input type="checkbox"/> ⁰ Very well <input type="checkbox"/> ¹ Slightly below par <input type="checkbox"/> ² Poor <input type="checkbox"/> ³ Very poor <input type="checkbox"/> ⁴ Terrible	B. Abdominal Pain <i>Please select one ...</i> <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Mild <input type="checkbox"/> ² Moderate <input type="checkbox"/> ³ Severe	C. Number of liquid stools today <div style="border: 1px solid black; width: 100px; height: 20px; margin-top: 5px;"></div>
D. Abdominal mass (Tummy feels lumpy / hard) <i>Please select one</i> <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Dubious <input type="checkbox"/> ² Definite <input type="checkbox"/> ³ Definite and tender	E. Complications <i>Please tick all that apply currently...</i> <input type="checkbox"/> ¹ Painful joints / arthritis <input type="checkbox"/> ¹ Anal fissure / fistula / abscess <input type="checkbox"/> ¹ Mouth ulcers <input type="checkbox"/> ¹ Skin nodules or ulcers (including pyoderma and erythema nodosum) <input type="checkbox"/> ¹ Eye pain or inflammation (red eyes) <input type="checkbox"/> ¹ Liver problems (eg. primary sclerosing cholangitis)	

SIMPLE CLINICAL COLITIS ACTIVITY INDEX (Walmsley et al 1998)

A. Bowel frequency (day) <i>Please indicate the number of bowel movements during the day</i> <input type="checkbox"/> ⁰ 1-3 <input type="checkbox"/> ¹ 4-6 <input type="checkbox"/> ² 7-9 <input type="checkbox"/> ³ more than 9	B. Bowel frequency (night) <i>Please indicate the number of bowel movements during the night</i> <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ 1-3 <input type="checkbox"/> ² 4-6
C. Urgency of defecation <i>Please select one</i> <input type="checkbox"/> ⁰ No hurry <input type="checkbox"/> ¹ Hurry <input type="checkbox"/> ² Immediately <input type="checkbox"/> ³ Incontinence	D. Blood in stool <i>Please select one</i> <input type="checkbox"/> ⁰ None <input type="checkbox"/> ¹ Trace <input type="checkbox"/> ² Occasionally frank (visible, obvious) <input type="checkbox"/> ³ Usually frank
E. General wellbeing <i>Please select one</i> <input type="checkbox"/> ⁰ Very well <input type="checkbox"/> ¹ Slightly below par <input type="checkbox"/> ² Poor <input type="checkbox"/> ³ Very poor <input type="checkbox"/> ⁴ Terrible	F. Extracolonic features <i>Please tick all that apply currently...</i> <input type="checkbox"/> ¹ Painful joints / arthritis <input type="checkbox"/> ¹ Anal fissure / fistula / abscess <input type="checkbox"/> ¹ Mouth ulcers <input type="checkbox"/> ¹ Skin nodules or ulcers (including pyoderma & erythema nodosum) <input type="checkbox"/> ¹ Eye pain or inflammation (red eyes) <input type="checkbox"/> ¹ Liver problems (eg primary sclerosing cholangitis)

The Epworth Sleepiness Scale (ESS)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = No chance of dozing

2 = Moderate chance of dozing

1 = Slight chance of dozing

3 = High chance of dozing

SITUATION	CHANCE OF DOSING
Sitting and reading	<input type="text"/>
Watching TV	<input type="text"/>
Sitting inactive in a public place (e.g. a theater or a meeting)	<input type="text"/>
As a passenger in a car for an hour without a break	<input type="text"/>
Lying down to rest in the afternoon when the circumstances permit	<input type="text"/>
Sitting and talking to someone	<input type="text"/>
Sitting quietly after a lunch without alcohol	<input type="text"/>
In a car, while stopped for a few minutes in traffic	<input type="text"/>
TOTAL	<input type="text"/>

Hospital Depression and Anxiety Scale (HADS)

Choose one response from the four given for each statement with reference to how you have felt over the last two-weeks. Please try to give your immediate response rather than thinking about their answers.

- | | | | |
|-----------|--|--------------------------|---|
| A1 | I feel tense or 'wound up': | | |
| | Most of the time | <input type="checkbox"/> | 3 |
| | A lot of the time | <input type="checkbox"/> | 2 |
| | From time to time, occasionally | <input type="checkbox"/> | 1 |
| | Not at all | <input type="checkbox"/> | 0 |
| D2 | I still enjoy the things I used to enjoy: | | |
| | Definitely as much | <input type="checkbox"/> | 0 |
| | Not quite so much | <input type="checkbox"/> | 1 |
| | Only a little | <input type="checkbox"/> | 2 |
| | Hardly at all | <input type="checkbox"/> | 3 |
| A3 | I get a sort of frightened feeling as if something awful is about to happen: | | |
| | Very definitely and quite badly | <input type="checkbox"/> | 3 |
| | Yes, but not too badly | <input type="checkbox"/> | 2 |
| | A little, but it doesn't worry me | <input type="checkbox"/> | 1 |
| | Not at all | <input type="checkbox"/> | 0 |
| D4 | I can laugh and see the funny side of things: | | |
| | As much as I always could | <input type="checkbox"/> | 0 |
| | Not quite so much now | <input type="checkbox"/> | 1 |
| | Definitely not so much now | <input type="checkbox"/> | 2 |
| | Not at all | <input type="checkbox"/> | 3 |
| A5 | Worrying thoughts go through my mind: | | |
| | A great deal of the time | <input type="checkbox"/> | 3 |
| | A lot of the time | <input type="checkbox"/> | 2 |
| | From time to time, but not too often | <input type="checkbox"/> | 1 |
| | Only occasionally | <input type="checkbox"/> | 0 |
| D6 | I feel cheerful: | | |
| | Not at all | <input type="checkbox"/> | 3 |
| | Not often | <input type="checkbox"/> | 2 |
| | Sometimes | <input type="checkbox"/> | 1 |
| | Most of the time | <input type="checkbox"/> | 0 |

A7	I can sit at ease and feel relaxed:		
	Definitely	<input type="checkbox"/>	0
	Usually	<input type="checkbox"/>	1
	Not Often	<input type="checkbox"/>	2
	Not at all	<input type="checkbox"/>	3
D8	I feel as if I am slowed down:		
	Nearly all the time	<input type="checkbox"/>	3
	Very often	<input type="checkbox"/>	2
	Sometimes	<input type="checkbox"/>	1
	Not at all	<input type="checkbox"/>	0
A9	I get a sort of frightened feeling like 'butterflies' in the stomach:		
	Not at all	<input type="checkbox"/>	0
	Occasionally	<input type="checkbox"/>	1
	Quite Often	<input type="checkbox"/>	2
	Very Often	<input type="checkbox"/>	3
D10	I have lost interest in my appearance:		
	Definitely	<input type="checkbox"/>	3
	I don't take as much care as I should	<input type="checkbox"/>	2
	I may not take quite as much care	<input type="checkbox"/>	1
	I take just as much care as ever	<input type="checkbox"/>	0
A11	I feel restless as I have to be on the move:		
	Very much indeed	<input type="checkbox"/>	3
	Quite a lot	<input type="checkbox"/>	2
	Not very much	<input type="checkbox"/>	1
	Not at all	<input type="checkbox"/>	0
D12	I look forward with enjoyment to things:		
	As much as I ever did	<input type="checkbox"/>	0
	Rather less than I used to	<input type="checkbox"/>	1
	Definitely less than I used to	<input type="checkbox"/>	2
	Hardly at all	<input type="checkbox"/>	3
A13	I get sudden feelings of panic:		
	Very often indeed	<input type="checkbox"/>	3

	Quite often	<input type="checkbox"/>	2
	Not very often	<input type="checkbox"/>	1
	Not at all	<input type="checkbox"/>	0
D14	I can enjoy a good book or radio or TV program:		
	Often	<input type="checkbox"/>	0
	Sometimes	<input type="checkbox"/>	1
	Not often	<input type="checkbox"/>	2
	Very seldom	<input type="checkbox"/>	3

CONFIDENTIAL

IBD Distress Scale

Today's date:

D	D	M	M	YEAR
---	---	---	---	------

Study Number _____

There can be many distressing aspects of inflammatory bowel disease (IBD) which can vary greatly. This scale is being designed to identify and measure distress related to IBD, including ulcerative colitis, Crohn's disease, Crohn's colitis and proctitis. To complete the questionnaire, please think about how your IBD has been making you feel **during the last three months**, whether the issues listed below cause you distress and if so, how much distress they cause you. IBD distress means 'physical or emotional burden or suffering' and is not the same as anxiety or depression. Please read each statement carefully and answer 'Yes' or 'No' in the relevant column. If your answer is 'Yes', please then circle the appropriate response on the scale to indicate how distressing the issue is for you. If a question is not applicable to you, please enter N/A in the 'No' column.

A	MEDICAL MATTERS	If yes, how distressing is this?							
		Yes	No	Mildly distressing			Highly distressing		
1	... I do not know what caused my IBD			1	2	3	4	5	6
2	... I feel disgusted by the symptoms of my IBD			1	2	3	4	5	6
3	... I feel embarrassed by the symptoms of my IBD			1	2	3	4	5	6
4	... I may need surgery for my IBD			1	2	3	4	5	6
5	... I may need a temporary or permanent stoma for my IBD			1	2	3	4	5	6
6	... I worry about how the disease will progress and how this will affect me			1	2	3	4	5	6
7	... I sometimes do not have access to IBD health professionals when I need it			1	2	3	4	5	6
8	... some of the health professionals I see don't always take my concerns seriously enough			1	2	3	4	5	6
9	... I worry that the treatment I am having for my IBD will not work			1	2	3	4	5	6
10	... I worry that my IBD treatment will cause unpleasant side-effects			1	2	3	4	5	6
11	... I feel that the side-effects of treatment are difficult to cope with			1	2	3	4	5	6
12	... I feel that the symptoms of IBD are difficult to cope with			1	2	3	4	5	6
13	... I worry that there is no cure for IBD			1	2	3	4	5	6

B	WORK, STUDY & CAREER	If yes, how distressing is this?							
		Yes	No	Mildly distressing			Highly distressing		
14	... I feel that IBD has reduced my opportunities in life			1	2	3	4	5	6
15	... it is difficult to talk to my employer, work colleagues or fellow students about my IBD			1	2	3	4	5	6
16	... I worry about how I will cope financially if I am unable to work			1	2	3	4	5	6
17	... I feel that my IBD causes me to let other people down			1	2	3	4	5	6
18	... I worry about the future (planning for a career or ongoing education)			1	2	3	4	5	6

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IBD Distress Scale

Today's date:

D	D	M	M	YEAR
---	---	---	---	------

C	EVERYDAY LIVING & COPING	If yes, how distressing is this?							
I am distressed because ...		Yes	No	Mildly distressing				Highly distressing	
19	... I worry about how other people will react if they find out I have IBD			1	2	3	4	5	6
20	... IBD takes up too much of my mental energy every day			1	2	3	4	5	6
21	... IBD takes up too much of my physical energy every day			1	2	3	4	5	6
22	... IBD controls my life			1	2	3	4	5	6
23	... I find the uncertainty of the disease difficult, i.e. not knowing how the disease will be from day to day or week to week			1	2	3	4	5	6
24	... I feel overwhelmed by the demands of living with IBD			1	2	3	4	5	6
25	... I feel burnt out by the constant effort needed to manage my IBD			1	2	3	4	5	6
26	... I worry that I will feel less happy about my body image if I have surgery			1	2	3	4	5	6
27	... I worry that when I am stressed about IBD, I make my symptoms worse			1	2	3	4	5	6
28	... I feel that IBD prevents me from being the person I <i>used</i> to be			1	2	3	4	5	6
29	... I feel that IBD prevents me from being the person I <i>want</i> to be			1	2	3	4	5	6
30	... I feel that IBD prevents me from doing the things I <i>used</i> to do			1	2	3	4	5	6
31	... I feel that IBD prevents me from doing the things I <i>want</i> to do now			1	2	3	4	5	6
32	... I feel that IBD makes me less attractive			1	2	3	4	5	6
33	... I feel that IBD negatively affects my intimate relationships			1	2	3	4	5	6
34	... I have less self-esteem now that I've been diagnosed with IBD			1	2	3	4	5	6
35	... I feel alone because of my IBD			1	2	3	4	5	6
36	... I feel fatigued and unable to think straight much of the time due to my IBD			1	2	3	4	5	6
37	... fatigue makes it difficult for me to be motivated to do the things I want or need to do			1	2	3	4	5	6

D	FAMILY & FRIENDS			If yes, how distressing is this?							
I am distressed because ...			Yes	No	Mildly distressing			Highly distressing			
38	... my friends don't appreciate how difficult living with IBD can be					1	2	3	4	5	6
39	... my family doesn't appreciate how difficult living with IBD can be					1	2	3	4	5	6
40	... my family doesn't give me the emotional support I would like					1	2	3	4	5	6
41	... it is difficult to talk to friends or family about my IBD					1	2	3	4	5	6
42	... I feel that other people sometimes do not understand I am unwell					1	2	3	4	5	6
43	... I worry about the impact my IBD has on the rest of my family					1	2	3	4	5	6
44	... I worry that any children of mine might develop IBD					1	2	3	4	5	6
45	... of thinking about the future (planning for a family)					1	2	3	4	5	6

CONFIDENTIAL

IBD Distress Scale

Today's date:

D	D	M	M	YEAR
---	---	---	---	------

E	SOCIAL SITUATIONS	If yes, how distressing is this?							
		Yes	No	Mildly distressing				Highly distressing	
46	... that social situations can be uncomfortable because of my IBD			1	2	3	4	5	6
47	... when I feel that my IBD causes me to let other people down			1	2	3	4	5	6
48	... that I often feel concerned about food and eating			1	2	3	4	5	6
49	... that important life events (wedding, holiday) may be disrupted by my IBD			1	2	3	4	5	6
50	... when I feel that I am a burden on other people because of my IBD			1	2	3	4	5	6
51	... that whenever I leave the house, I worry that I may have a bowel accident or pass loud or smelly wind			1	2	3	4	5	6
52	... that whenever I leave the house, I worry about where the toilets are			1	2	3	4	5	6
53	... that I may have to wear protective pads in my underwear because of bowel accidents			1	2	3	4	5	6
54	... when I am in a crowded public place			1	2	3	4	5	6
55	... when I am taking part in a sporting activity, or going shopping, to the cinema, or to a concert			1	2	3	4	5	6

56	On a scale of 0 to 6, where 0 is 'Not distressed' and 6 is 'Highly distressed', how would you rate your current level of distress? <i>Please circle one option</i>						
	0	1	2	3	4	5	6
Not distressed							Highly distressed

57	Please indicate your current level of disease activity: <i>Please circle one option</i>			
	In remission	Mild flare	Moderate flare	Severe flare

Finally, please identify the three issues causing you the most distress at the moment, and write them in the boxes below	
1.	
2.	
3.	

Perceived Stress Scale (PSS)

The questions in this scale ask you about your feelings and thoughts during THE LAST MONTH. In each case, please indicate your response by placing an "X" over the circle representing HOW OFTEN you felt or thought a certain way.

	Never	Almost Never	Sometimes	Fairly Often	Very Often
	0	1	2	3	4
1. In the last month, how often have you been upset because of something that happened unexpectedly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. In the last month, how often have you felt that you were unable to control the important things in your life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. In the last month, how often have you felt nervous and "stressed"?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. In the last month, how often have you felt that things were going your way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. In the last month, how often have you been able to control irritations in your life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. In the last month, how often have you felt that you were on top of things?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. In the last month, how often have you been angered because of things that were outside your control?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Managing your Inflammatory Bowel Disease Fatigue

A Cognitive Behavioural Therapy Manual

Developed by

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Introduction

This manual provides information about how to manage fatigue (extreme tiredness) for people with Inflammatory Bowel Disease (IBD). There is no 'one size fits all' treatment for IBD-fatigue. However, good evidence says that changing your lifestyle and the way you do activities may reduce your fatigue. Making these changes may also help you better manage your other IBD symptoms.

The information in this manual is based on medical research from universities, hospitals and charities around the world. It also draws on real life experiences of people with IBD-fatigue.

We do not yet fully understand IBD-fatigue because the medical factors that cause fatigue are unclear. There are also a number of other non-medical factors, which also play a part. The information in this manual includes what we already know about IBD-fatigue and what we think contributes to it. There will be material and activities for you to do, based on the factors that lead to IBD-fatigue. We aim to help you to better manage your symptoms and reduce your fatigue.

Using the Manual

This manual is part of an 8-week programme. A therapist will work through the eight sessions with you in the following way:

- You choose whether your sessions will take place over the telephone or Skype
- The first session will be 60 minutes
- The next seven sessions will be about 30 minutes each
- It is important that these sessions are held at a time when you can talk privately and uninterrupted for the entire session
- It is also important that you have your manual with you during all of the sessions, as it is a guide for the programme. Feel free to write in the manual to focus your thoughts
- Feel free to ask any questions and to discuss your goals/tasks for the week with your therapist

Your sessions have been scheduled with (name of therapist) as follows:

Session 1 – Telephone on

Session 2 – Telephone on

Session 3 – Telephone on

Session 4 – Telephone on

Session 5 – Telephone on

Session 6 – Telephone on

Session 7 - Telephone on

Session 8 – Telephone on

To change your session(s), please contact (name of therapist):

- by Telephone:
- by Email:

If you have any other questions or issues throughout the study, please contact Micol Artom:

By Telephone: 079 30237160, by Email: micol.artom@kcl.ac.uk

In this binder you will find:

- This manual
- A different coloured booklet for each of the sessions
- A Homework booklet

Each session has a lot of content. Most of it will be covered as we work through it. However, it is your choice how to use the manual. For instance, you may choose to read parts of it before your session or you may choose to read it again after your session.

You may find that some of the material will apply to you more than other parts. This is because your experience of IBD and fatigue is individual and unique to you.

Each session combines information with a series of activities to fit into your day-to-day schedule. The time to do these tasks should usually *take no more than 20 minutes per day, but this may vary from person to person.*

Research has shown that even simple changes may make a difference to your symptoms. When you stick to the programme and to your own personal goals it is more likely for your symptoms to change for the better. Therefore, it is important that you commit to fitting the suggested activities into your daily life.

To help you do this we have provided a Homework booklet, with homework sheets. These can be completed at each session and help you record your progress by filling in information related to you. Be sure to look at the session number at the top of each homework sheet. If you have any doubts, your therapist can guide you through how to fill in the sheets.

In the last session, we will ask you to give us the Homework booklet so that we can copy it and record how much you were able to complete. This information is important for the study but will not reflect on you in any way.

We want you to be comfortable. So if you feel the information is too personal you can choose not to share it with us.

Session 1: IBD-Fatigue Explained

This week we will cover:

- 1) Understanding IBD-fatigue
- 2) A model for IBD-fatigue
- 3) Your symptoms
- 4) Setting your goals and homework tasks

1) Understanding IBD-fatigue

This section will describe some of the factors that lead to fatigue in IBD.

Fatigue is one of the most common but least understood symptoms of IBD.

We will explain the following:

- what fatigue is
- what might cause fatigue
- what might contribute to and maintain fatigue in IBD

Much of it will probably be familiar to you, and not all of it will directly apply to you. However, please read through all the sessions of the manual so that you can get an overview of fatigue.

What is IBD-fatigue?

IBD is a chronic life-long inflammatory illness of the gut. Crohn's disease (CD) and Ulcerative colitis (UC) are the two main forms of IBD. IBD affects more than 300,000 people in the UK. People can experience a wide range and variety of symptoms with IBD, but fatigue is very common. Often it is one of the most distressing symptoms. People who experience IBD-fatigue report that it:

- beyond just tiredness
- is a state of exhaustion
- can impact on their ability to get through the day
- can lead to limiting or missing social events
- can influence their decision not to work or take early retirement
- can be physical and mental
- can be acute or persistent
- is complex and influenced by many different things

The pattern of fatigue (and of symptoms in general) varies. It can be present even at rest, and can be made worse by physical or mental effort. Walking to the local shops, reading a book, doing the washing-up, writing a letter, and talking to family or friends can become exhausting tasks, needing huge amounts of effort.

One person described fatigue as:

“It’s like somebody’s drained all the blood out of you”.

It is common for a number of aspects of daily life to be affected. Many people have to cut down on, change or give up some activities altogether. Extra rest is often needed before and/or after any activity. Often, this fatigue and the limitations it can cause to everyday life can also mean you feel upset, frustrated and have low mood. This is completely understandable.

Talking about fatigue: how is it described?

- Brain fog
- A big black hole
- Being woozy or fuzzy
- Zombie mode
- Overwhelming heaviness
- Just shattered
- Completely wiped out

Why do I feel so tired?

Fatigue is one of the least understood symptoms of IBD. The specific medical factors that cause IBD-fatigue are unclear so, we still don’t know exactly what causes it. There are also a number of other factors which contribute to and maintain fatigue.

These factors include:

- our behaviour, i.e. what we do
- the way we think
- our emotions
- the environment

We will discuss each of these one by one.

Medical factors causing fatigue:

There is some evidence for medical factors which contribute to fatigue.

Inflammation and fatigue

IBD causes inflammation in the gut, mostly the small intestine and/or the colon. The body fights the inflammation in various ways. Fatigue in people with IBD may be caused by the way the body responds to inflammation.

Anaemia and fatigue

Fatigue is sometimes related to anaemia. Anaemia is a common issue with IBD. It is caused by blood loss, diarrhoea, and failure of the body to hold on to nutrients. Without enough iron, folic acid and vitamin B12, your body can't make more red blood cells. If your IBD is in remission and you are still fatigued, you may want your doctor to do a blood test to check for anaemia and lack of vitamins.

Behaviour in causing fatigue:

It is difficult to cope with unexpected, prolonged and/or severe fatigue. If you have had severe fatigue or fatigue for a long time you may have tried to manage it by resting more and avoiding or reducing activity. This may be because you hope to feel better and want to stop fatigue from getting worse. You might then push yourself to do as much as possible when you are feeling better and decide to rest more when your symptoms get worse. This is what we call 'all-or-nothing' behaviour.

These are natural, understandable attempts to manage your fatigue, and sometimes seem to be the only possible solution. However, these behaviours can actually contribute to the vicious cycle of symptoms and disability.

a) Can I rest too much?

When you experience severe fatigue and pain for a long time, your natural response may be to rest more, and cut back or modify your activity. Rest is a very effective way of being less tired and having fewer symptoms in the short term. However, in the long term, it may be less helpful. If you rest too much you will be less able to do exercise which can make you weaker by making your muscles less strong. It can also cause heart and breathing difficulties, which make activity more difficult. This means that even at lower levels of activity you can have more pain and fatigue.

So, while rest may seem helpful at first, the next time you try an activity you may realise its negative effects. These include immediately having more symptoms or having them later on, which worsen with continued activity.

Not surprisingly, when you feel repeatedly exhausted and experience pain you may wish to avoid, reduce or control these experiences. As a result, if you have more symptoms you may see it as a signal to cut back on activity. Since resting for a long time seems to be the only way to prevent symptoms from becoming worse, it may make your life feel more restricted.

b) What happens with all-or-nothing behaviour?

You may have tried to control and manage your symptoms by trying to fight through and ignore the fatigue. Such attempts are usually short-lived, as you are left feeling even more exhausted and unwell.

Since neither too much rest nor activity seem to help, you may learn to cope with your symptoms by doing as much as possible when you can. This can often lead to over-tiring yourself in the process. You may then decide to rest more when your symptoms get worse. Alternating between over activity on a 'good day' and under-activity on a 'bad day' may appear to prevent extremes of disability. Yet it can often lead to worse fatigue and disability.

Since any activity you do is "paid for later", this can be as upsetting and restricting as complete rest.

Thinking in causing fatigue:

Another factor that may impact on fatigue is the way you think about yourself and your illness. For example, you might think you will never cope with your symptoms all the time. It is easy for a chronic illness to bring on unhelpful ideas and thoughts, which in turn influence the way you make sense of your symptoms.

Unhelpful ideas can also lead to lower mood or anxiety, and lead to less helpful behaviour. Unhelpful thoughts can trap you in a vicious cycle where the more fatigued you become the more unhelpful thoughts you might have. The more you believe them, the more tired you might become.

For example, one woman talked about how whenever she experienced some symptoms she would think "I can't stand this", "this is never going to go away", and "I have no control over this". In turn she felt hopeless and low in mood. She then focused even more on her symptoms, and had more unhelpful thoughts.

The specific symptoms of these mood states (like depression) can overlap and make symptoms of IBD and fatigue worse. They can also affect how you cope.

Fear of making fatigue worse and fear that too much activity may lead to a relapse is common in IBD. You may also worry that symptoms are a warning sign; or that continued or repeated activity may be harmful. All of this can leave you feeling helpless and uncertain.

Since chronic illness is often hard to predict, anxiety about coping, doing certain activities or reaching your goals is common. Being depressed and down will make you more likely to do less activity. On the other hand, frustration is more likely to make you do too much too quickly.

Embarrassment and shame are also linked with IBD-fatigue. They can cause you not to go out as much socially, to do less activity and may contribute to low mood as well.

Environment in causing fatigue:

Your experience of IBD and fatigue can also be influenced by environmental factors such as stress and reactions from those around you.

Stress can often have an effect on fatigue. Some controllable stressors, such as your work, may be dealt with or changed in some way. Uncontrollable stressors, such as how your illness might progress, are more difficult to manage. Trying too hard to change uncontrollable stressors can lead to more fatigue.

Another environmental factor is the advice and reactions from others. A lot of distress can be caused by unhelpful or inappropriate reactions from others. Perhaps they do not understand IBD, do not take your fatigue seriously, or are too worried about you. The support of family, friends, doctors and colleagues is very important. However, it can sometimes be difficult for others to understand what is wrong, especially when there aren't many clear signs of illness or fatigue, or if they see you on a "good" day.

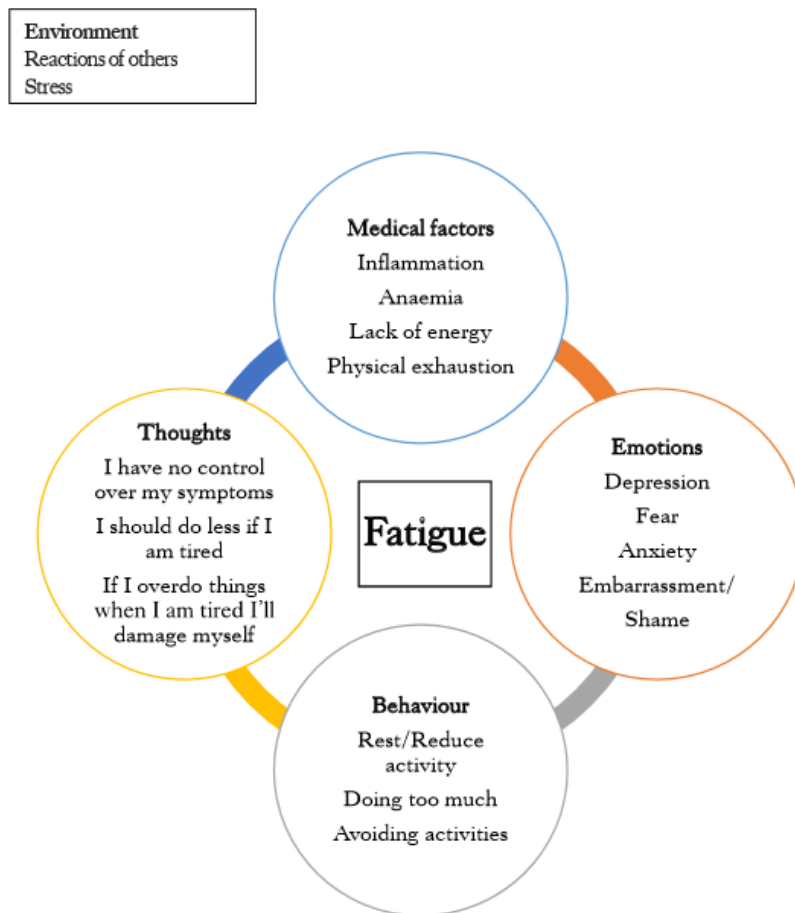
Other people's views of any chronic illness can be mixed. People may see illness as being either physical ('real') or psychological ('all in the mind'). This is an unhelpful way of seeing things, since all illnesses involve a mix of physical and psychological factors. You may have had some negative reactions from others. This can add to emotional distress and may be having an impact on your fatigue.

2) A model for IBD-fatigue

As we said in the previous section, a helpful way to understand IBD fatigue is that, in addition to the medical side there are other factors that also contribute to and maintain fatigue. These include emotional, behavioural, environmental, physical and the way you think.

You may have noticed that there is a lot of overlap between the different factors, and that change in one area may lead to change in another. This is exactly what we are saying. Fatigue is likely to be affected by a number of different aspects and change in one area will affect other areas. We have drawn the different fatigue factors into a model to make it clearer.

Example: A model for IBD-fatigue



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This model is useful because it separates the medical factors that cause fatigue, from the factors that contribute to fatigue.

One of the goals for treatment is to: figure out what happens to you when you get fatigued, think about how your experience might relate to this model and find new or more helpful ways to better manage your fatigue.

Today we will look at how this model applies to you and your symptoms. Next week we will introduce an approach called “Cognitive Behaviour Therapy” (CBT). CBT is a treatment to help you manage your fatigue, with the aim of reducing it.

3) Assessment of your symptoms

In order to design a successful treatment plan, it is important to identify activities and thoughts that may be working against you managing your fatigue. For the programme to work well it must suit your needs.

In this section we will talk about your own personal experiences with IBD and fatigue and how you have managed your symptoms so far. Everyone has different ways of dealing with their illness. We call these 'coping skills'.

For example, some people may try to ignore their symptoms and carry on as normal. Other people may avoid certain situations, which they believe make their symptoms worse. It is important that you develop coping skills that help you manage your symptoms better and that you work towards changing any unhelpful coping skills.

Some questions

The following questions will help us understand how IBD impacts on you and what you have done to manage symptoms so far:

1) What IBD symptoms do you experience? Which one(s) do you find the most distressing?

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.....

.....

.....

2) How would you describe your experience of fatigue? How much of a problem is it for you?

.....

.....

.....

.....

3) How do you usually manage your IBD symptoms? How do you usually manage your fatigue? What have you found more helpful? What have you found less helpful?

.....

.....

.....

.....

4) Do you worry about anything in relation to your illness and symptoms? If so, what?

.....

.....

.....

.....

5) Does anything make you feel down or depressed in relation to your illness and symptoms? If so, what?

.....

.....

.....

.....

6) Have you stopped doing anything due to your IBD symptoms? If so, what? Have you stopped doing anything because of fatigue? If so, what?

.....

.....

.....
.....

7) How do your family/friends respond when you feel fatigued?

.....
.....
.....
.....

Your goals for treatment

Let's discuss what you would like to achieve from this programme in order to manage your fatigue.

Please use the space provided to note down your own personal goals. What would you gain if you were less fatigued?

.....

.....

.....

4) Setting homework tasks

Part of our treatment approach asks that you complete 'homework' tasks between sessions. These are small activities for you to focus on, and can involve:

- reading
 - keeping track of your symptoms or your mood
- or*
- experimenting with new strategies that have been discussed during the session

At the start of each new session we will discuss how you got on with the homework tasks, and what you found helpful and unhelpful. You will find the tasks in the Homework booklet at the end of the manual.

Tasks from Session 1

Today we have introduced a lot of new information about IBD-fatigue, and it may be helpful for you to read this section again.

Next week we will talk about the CBT approach. It will be helpful for you to read the information about CBT at the beginning of the next session.

Do you have any questions before we finish today?

.....

.....

.....

.....

Session 2: CBT for IBD-Fatigue

This week we will cover:

- 1) Key points and questions from last week
- 2) Reviewing your homework
- 3) Cognitive Behaviour Therapy for IBD-fatigue
- 4) This week's homework task: self-monitoring

1) Key points and questions from last week

In the first session we gave you a lot of information about the factors leading to fatigue and introduced you to a fatigue model. Was there anything important from last week's session that you would like to discuss?

.....

.....

.....

.....

2) Reviewing the homework

Over the last week you may have re-read the information from the first session. Are there any questions that you about any of the information from last week's session?

.....

.....

.....

.....

You may have also read the information about Cognitive Behaviour Therapy (CBT). We will look at this approach in a bit more detail today. If you have any questions from your reading, perhaps we could answer them when we cover this section.

3) CBT for IBD-fatigue

Last week we looked at the factors which might lead to and maintain fatigue in IBD. We can use this knowledge as a basis for a simple and effective CBT treatment plan to help you better manage your symptoms.

In this section, we will explain what CBT is all about, and what treatment will look like.

What is CBT?

CBT is a psychological therapy, which relies on your active participation. It uses a range of techniques to change and overcome any factors that contribute to your problems or make your recovery more difficult. CBT has been used successfully for a variety of illnesses. These

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include chronic fatigue syndrome, chronic pain, arthritis and heart disease. People with other fatigue illnesses have found that CBT has helped to reduce their fatigue.

What does CBT for IBD-fatigue involve?

The aim of this treatment is to develop more helpful ways to manage your fatigue and reduce its severity. In IBD-fatigue, treatment involves strategies to reduce your disability and better manage your symptoms.

You have probably already used some strategies that help you cope with your IBD. Some of your strategies may be helpful and some may be unhelpful. CBT will help you to identify and replace any unhelpful things you do, and offer you new techniques to reduce the effect fatigue and related symptoms have on your quality of life. So, the aim of CBT is to build on your own strengths and positive coping techniques.

The sessions are suited to your needs. Therefore, the first step is to build up a picture of your own symptoms and experiences of fatigue.

This will include looking at your patterns of:

- rest
- sleep
- activity
- fatigue

We will then discuss exactly what you feel you can and can't do each day.

We will also cover other strategies such as:

- understanding your IBD symptoms
- learning how to identify unhelpful or negative thinking patterns and how to replace them with more helpful ones
- relaxation or sleep control techniques
- managing stress
- coping with emotions

The treatment sessions:

- are structured and take place over 8 weeks
- are individual sessions with the same therapist throughout treatment
- are collaborative which means that we work together as a team

Please remember:

Regular calls are very important, to keep momentum and consistency of treatment. Of course, you can go on holiday. This is often a good opportunity to practice what you have learned in a different setting. But, as far as possible, try to avoid too many unplanned absences.

How are the sessions structured?

At each session, you will set targets for the week ahead. At the beginning of the session we will review your progress and discuss any difficulties you may have had. During the session you will decide what areas you wish to work on during the coming week, what "homework" tasks you want to set, and how you will achieve them.

How will my progress be measured?

To make sure your treatment is going in the right direction for you, we will often measure your personalised progress. We will ask you to complete a "package" of questionnaires (some of which you may have already completed) that measure the severity and impact of your illness.

You will be given the questionnaire package to fill in at the start of your treatment, at the end of your treatment and at 6 and 12-months following your treatment.

We realise that we are asking you to fill in a lot of questionnaires. By completing them you help us with the linked research to see if the treatment works. It also allows us to give you feedback about your personal progress.

What happens when treatment ends?

One of the most important aims of CBT is for you to become your own coach, and to continue with your treatment programme once your 8 sessions are completed. This is very important. Your continued work will help you to improve upon your gains, even after the end of your treatment plan.

After your final session, you will be contacted by a member of the research team, and followed up at 3, 6 and 12-month intervals after your treatment has ended. This follow-up will help us to understand whether you feel you have benefited from treatment and whether you have been able to maintain or even improve on this during the follow-up period.

The role of family and friends

This is a self-directed treatment, where you carry out most of the work by yourself. Many people find it helpful to involve a close friend or relative as a support person though. This means you'll have someone who you can talk things over with and who understands what you are doing in treatment. Their main role is supportive. This can be very important since CBT can require quite a lot of commitment. There may be times when you feel like giving up, or when you feel as though you are making no progress. At such times, someone who can encourage you and support your achievements can be very helpful.

Even if you do not involve other people in your treatment directly, it can be useful for them to know what it involves, so that they do not worry about you.

You may choose to give your support person(s) part of the manual to read. This may help them understand what you want to achieve.

4) Homework task: self-monitoring

Now that we have a better idea of your symptoms and how you have tried to cope with them, we would like you to use a self-monitoring fatigue diary. In the diary, you will track your activities, time of rest and experience of fatigue between this session and the next session.

Self-monitoring

Keeping a diary can help you build up a true picture of your fatigue in relation to your daily activities and routine. Your diary might help make you more aware of patterns, differences or irregularities in your activities. It will also show how your fatigue varies from day to day, what contributes to your symptoms, and how you respond. This information will be important for planning and knowing how to best manage your difficulties.

Filling in your self-monitoring fatigue diary

Your diary is on the next page. For the next week, please use the diary sheet to write down what you have done four times a day (morning, midday, afternoon and evening). For example, this may include doing the housework, working, sleeping, attending a social event, or having dinner. Please also write down the times that you wake up and go to bed.

It is important to record both rest and activity. It is also important that you are detailed about what you actually do. For example, if you spend an hour sitting in a chair looking out of the window, please state this exactly rather than simply writing 'resting'. When you fill in your activity record, please also write down how fatigued you feel using the scale below.

Fatigue:

^	^	^	^	^	^	^	^	^	^	^
0	1	2	3	4	5	6	7	8	9	10
None			Mild		Moderate			Severe		

Keeping records may seem a bit overwhelming at first so it may be easier to fill them in as you go. For example, you could fill them in during mealtimes and before you go to bed. This will avoid you having a backlog of things to remember at the end of the day.

It should not take any longer than a few minutes each day to fill in your diary.

Below is an example diary log:

	MON	TUES	WED	THURS	FRI	SAT	SUN
Wake up time	6am	9am	8am	6am	10am	12pm	10am
Morning	Breakfast, take kids to school	In bed	Breakfast, housework	Breakfast, take kids to school	Breakfast, visit friend	Asleep	Watch TV
Fatigue	F=5	F=4	F=4	F=5	F=4		F=5
Midday	Prepare lunch, housework	Walking, watch TV	Resting	Lunch, shopping	Walking, lunch	Gardening	Shower
Fatigue	F=6	F=4	F=5	F=5	F=4	F=4	F=5
Afternoon	Resting,	House work	Visit friend	Resting	House work	Visit friends	Prepare dinner
Fatigue	F=4	F=4	F=4	F=4	F=5	F=7	F=4
Evening	Dinner, watch TV	Dinner, reading	Pick up kids, dinner	Get takeaways	Dinner, Watch TV	Rest	Walking, dinner
Fatigue	F=5	F=3	F=4	F=6	F=4	F=5	F=3
Bedtime	9pm	1am	9pm	8pm	12am	9pm	12am

Self-monitoring can be challenging at times. Can you think of anything that might get in the way of completing this task?

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What ideas do you have that might help you overcome these possible obstacles?

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Do you have any questions before we finish today?

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Session 3: Activity Scheduling

This week we will cover:

- 1) Key points and questions from last week
- 2) Reviewing your Self-Monitoring Fatigue Diary
- 3) Patterns of rest and activity and its effects on the body
- 4) Planning activity and rest
- 5) Homework

1) Key points and questions from last week.

What questions or comments did you have after last week's session? Let's spend a few minutes discussing them first.

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2) Reviewing the Self-Monitoring Fatigue Diary

Hopefully you had a chance to complete your self-monitoring diary in the previous week. Let's discuss what you noticed from using it:

Were there any patterns in your activities and fatigue levels?

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How much time did you rest?

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What did you do when you felt fatigued?

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What did you do when you did not feel fatigued?

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Was there any time of the day or a certain activity that made your fatigue worse?

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What is your sleeping pattern like?

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How much did you rest during the day?

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3) Patterns of rest and activity and its effects on the body

Your activity schedule has told us something about your patterns of rest and activity, and how they relate to your fatigue. Today's session focuses on this in more detail.

As we discussed in the last session, people who experience severe fatigue and/or experience fatigue for a long time often try to manage it in two ways. They rest more and reduce activity in the hope of feeling better and to prevent their fatigue from getting worse. They may also push themselves to do as much as possible when they can and rest more when symptoms get

worse (all or nothing behaviour). Many people use all of these strategies. They are natural, understandable ways to try to manage fatigue.

Reasons why too much rest or extremes of rest and activity are less helpful in the long run:

- a) Rest for short-term problems can be helpful, but for long-term problems, it is not very helpful. In fact, if you rest too much your body becomes unfit. After periods of rest and less activity, the heart becomes less fit, causing symptoms like rapid heartbeat, sweating and nausea.
- b) If you do less activity, your physical ability for exercise is reduced and you may experience shortness of breath and fatigue. Less activity then increases the feeling of fatigue when you do exercise. With continued rest and less activity your body copes with less and less activity over time.
- c) Rest and less activity leads to less muscle tone in your legs, which causes less blood going back to your heart. This causes a drop in your blood pressure when you stand up and less blood going to your brain. This then leads to unpleasant symptoms like feeling dizzy and fatigue.
- d) People tend to make decisions about their rest based on their fatigue levels and/or symptoms rather than keeping their rest constant. This means that your body never has the chance to get used to a regular routine of rest and activity. Too much rest can make you feel even more tired, have less motivation, and can ruin the quality of your sleep.
- e) When you push yourself in order to catch up on things your symptoms may get worse, causing you to slow down or to rest completely. As a result, you get behind even more and as soon as you feel better you push yourself really hard to catch up on things again. In time the cycle repeats where symptoms re-emerge and you are forced to rest again.
- f) All-or-nothing people often find ways to do things they feel they have to get done such as work tasks and/or care-giving for children. They tend to cut out fun or relaxing activities when they experience symptoms. This means they usually miss out on activities which they think are 'for themselves'. Because of this, they can start to feel depressed or overly stressed and anxious.

Looking at your activity schedule do you think any of these patterns are contributing to your fatigue?

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4) Planning activity and rest

We have discussed the patterns of rest and activity in your week from the activity diary, and the reasons why they may not be very helpful for managing fatigue in the long term. Now let's see if we can make activity and rest a more consistent part of your daily routine, rather than it being dependent on your symptoms or level of fatigue. Some of you may need need to work on slowly increasing activity levels, alternatively you may need to try to reduce the amount you do. Or may need to focus on consistency.

Before we do this, do you have any concerns about starting regular activity? Let's take a few minutes to discuss these.

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Some tips when changing activity patterns

There are some key things to remember when setting goals to change your activity patterns. These include:

- Your goals should work towards helping you become consistent in your activities rather than 'symptom-dependent'. This means, you need to make sure you don't do too much on a good day or too little on a bad day. Remember that doing too much on a good day will often contribute to you having a bad day.
- You can reach consistency by scheduling your days so that **you do a similar amount every day**. It is important to try to schedule a balance of work-related activities, activities for other people, rest or relaxation periods and time for yourself.
- It will be more challenging to carry out your activities on bad days. But, by sticking to your routine you will start to gain control over your symptoms rather than allowing your symptoms to gain control over you.
- Your activity patterns have often developed over a long time and it will take time and effort to change them. So, try not to be too hard on yourself. It is important that you acknowledge any small changes you make.
- It is important that you **make changes slowly and steadily** over the next weeks, rather than changing activity patterns too quickly. This will help to maintain the changes long term.

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Setting your goals

A) Using a goal sheet

It is really important to plan in advance what you are going to do each day, by creating a weekly goal sheet. **The aim for this week is for you to do the same amount of activity, and rest the same amount every day no matter how you feel.** So whether it is a good or bad day you still rest the same amount. This will help you develop a consistent pattern of rest and activity, which is important for managing fatigue and other symptoms.

B) Setting realistic activity goals

Part of your goals include developing helpful activity patterns. Therefore, you'll need to schedule some type of aerobic exercise. This is any activity where your breathing and heart rate goes up to deliver oxygen to the muscles, which allows them to work well. This will help strengthen your body and should improve the quality of your sleep.

Activities can involve walking, stair exercises, bike sessions, dancing, jogging, and swimming. It is important to choose something that is realistic and that you enjoy. You should aim to do something every day for a similar amount of time. Over the next few weeks, we will work towards increasing this to a level, which is comfortable and suitable to your individual situation.

What ideas do you have about activities you would like to try?

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The most important thing is to make sure your initial goals are realistic and achievable so that you can reach a consistent pattern during the day and the week. Your activity schedule from last week can give us an idea of what you were already doing. We can use this as a starting point by setting an initial activity goal that is a little less than before. The aim is that it is daily and consistent.

Some examples of goals other people have set for themselves at the beginning include:

- To wake up by _____ (fill-in appropriate time) every day
- To walk for 5 minutes 3 times a day at 10 am, 2 pm and 7 pm
- To rest for 15 minutes in the morning and afternoon
- To go to bed by _____ (fill-in appropriate time) every day

So, over the next few weeks, the idea is to increase your exercise and activity time in a consistent controlled manner. At the end of the session, we can spend a bit of time going through these together by filling in your planned activity goals in your goal sheet.

C) Setting realistic resting goals

Rest after exercise is important because it allows time for your muscles and your heart to recover before the next activity. Rest also allows your body to relax. The best position for resting is sitting down and/or using cushions to prop up the upper body to avoid lying down for a long time. This is because lying down for too long makes your muscles weaker.

The important thing is to schedule rest in a consistent way. So instead of resting when you feel tired or fatigued, the idea is to plan rest at set times during the day for set amounts of time. Again, we can start-off by looking at your activity schedule from last week to make sure that you are planning enough rest to get through the day.

Ideally try to avoid resting for more than 30 minutes. Sitting for longer will lead to more unpleasant symptoms when you stand. After your timed exercise, rest until the symptoms of deconditioning (legs shaking, heart beating fast) have stopped. As the weeks go by, your aim is to reduce your rest time after activity to 25 minutes, then 20 minutes etc.

So, over time, as exercise and activity goes up, rest time goes down.

What would be a good 'rest time' be for you to start-off with?

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You might like to write this in your goal list at the end of this session.

D) Predicting set-backs

A temporary increase in fatigue-related symptoms can happen when you start to plan rest and activity. This is normal and is just your body getting used to a new routine of planned consistent rest and activity. You might be tempted to reduce your activity or increase your rest. But if you do this you will be returning to the same behaviour that was making you fatigued. It's really important that you try to stick with your chosen goals. Once your body has become used to the pattern, the discomfort will lessen and you will be ready to take the next step. However, if you experience a true relapse of your IBD, you may decide to cut back on your activity.

As we said earlier, it is normal to have set-backs when you start a programme like this. Setbacks can include:

- doing too much activity because it's a good day
- a stressful event occurring
- something unexpected occurring and having to do activities other than your regular activity programme
- feeling unwell and deciding to reduce your activity level and resting more than you planned

When things like this happen, try not to get too upset. Aim to do the same amount of activity as the day before, but no more. Start to do more again as per your planned schedule the next good day. It is also important to remind yourself that carrying on in a controlled gradual way will do no harm. In fact, it will give you the physical benefits of exercise and reduced symptoms.

So, remember you can expect setbacks. The most important thing is to remind yourself this is normal, and try as far as possible to stick to your pre-planned goals. Remember it is the overall change over the weeks that is important, not the odd few bad days.

5) Homework

Today we have discussed how reduced activity and too much rest can maintain fatigue, why changing these patterns might be helpful, and how this can be done. The last step is to put it into practice.

Tasks for this week:

- Write your personal goals on your goal sheet.
- Try to meet as many of your targets as possible
- Keep a record of your achievements.
- Next week we will be covering sleep and managing stress. You may like to read these sections before the next session.

Do you have any questions before we finish today?

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Session 4: Improving your Sleep

This week we will cover:

- 1) Key points and questions from last week
- 2) Homework review and setting new targets
- 3) Improving your sleep
- 4) Diaphragmatic breathing
- 5) Homework for next week

1) Key points and questions from last week.

Last week we discussed the importance of planning activity, rest, and sleep. We also discussed how this can have an impact on managing fatigue. Have you had any questions or thoughts since then?

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2) Homework review and setting new targets

Over the last week you have tried using the goal sheet to record your activity levels and rest periods. What did you notice when you tried the new routine?

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How easy/difficult did you find it?

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Are there any things you would like to adjust or change?

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In terms of increasing your activity levels and reducing your levels of rest, what feels like a reasonable step to take next?

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You may like to write your new goals for the next week on another goal sheet (which you can find at the end of this session).

3) Improving your sleep

Sleep problems are common in IBD patients. Causes can include bladder problems, pain, anxiety and depression. If you experience fatigue, you may find that your sleep patterns can be disrupted, and this can add to your feeling of a lack of energy. So, this week we will find out a bit more about your sleep patterns and how you manage stress.

Looking at your activity schedule, what is your current sleeping pattern like?

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In the sections below we review some general tips for getting a good night's sleep. We also discuss some common problems people have with their sleeping and how you might like to address them if sleep is a problem for you. You might find some factors more relevant than others.

If you are a good sleeper you will be able to sleep without doing a number of the things we discuss. However if you are a poor sleeper you may need to be more careful. So, you might have to make more of an effort to make sure you are doing the things that are the most helpful for improving your sleep.

As we work through the next sections you may find it helpful to write down the things that you think might contribute to your sleep problems. Once you have done this it will make it easier to set personal goals in order to improve your sleep.

General tips for getting a good night's sleep:

- Only go to bed when you feel sleepy. If you try and fall asleep before your body is ready you will tend to lie in bed thinking thoughts that worry you.
- Your bedroom should be linked to the idea of sleep rather than being awake. Therefore, if you are unable to fall asleep or return to sleep within 20 minutes, get out of bed and go to another room. Try doing something relaxing like reading a book, listening to music, or a relaxation exercise. Return to bed only after you feel sleepy. This may feel like a hassle especially if you are leaving a nice warm bed, but it does make a difference.
- With the exception of sex, try to avoid doing all forms of activity in the bedroom such as watching TV, working or eating.
- Avoid stimulants such as coffee, tea, chocolate or chocolate drinks, fizzy drinks and cigarettes at least 4 hours before you go to bed. All of these might disrupt sleep.
- Many people think that alcohol helps them sleep because it relaxes them. It may help you to fall asleep, but it can also cause you to wake up during the night. So, it is better to avoid alcohol at least two hours before you go to bed.
- Simple things like a comfortable bed in a warm, quiet dark room, can all help to make sleep easier. Earplugs and eyeshades can also help.
- Regular exercise will help you sleep better. However, be sure to avoid energetic exercise just before going to bed as it can wake your body up and make it difficult to sleep.

Irregular sleep patterns:

You may find that you have a sleep pattern which varies from day-to-day. People who have difficulty sleeping may often go to bed earlier than usual on some days, sleep in later on others, or nap during the day to catch up on lost sleep.

Irregular sleep patterns such as these can confuse our internal body clock or natural bodily rhythm. This can create difficulties sleeping. Jetlag is a classic example of what happens when our body clock is disrupted. If you have ever experienced jetlag from long haul flights you will be aware of its symptoms. These include difficulty sleeping, feeling heavy, waves of extreme tiredness, difficulties remembering and problems concentrating.

Similar symptoms may occur if you have consistently restless or disturbed sleep, especially if this leads you to sleep at different times each day. A helpful solution for this is **to develop a consistent sleep routine**. This is very similar to the idea of building up a consistent routine around activity and rest. Research tells us that the way to do this is to:

- Go to bed and wake up at roughly the same times each day. Even if you have had a really bad night of sleep you should try and stick to this.
- Avoid napping during the day. Daytime sleep may help in the short term, but it often leads to sleep difficulties at night. If you like sleeping during the day try to distract yourself instead. It may help by taking a gentle walk or doing something relaxing.
- Make sure you wake up at the same time by setting an alarm clock; even if you have woken up several times during the night and even if you are feeling tired. Over time this approach will help you sleep better.

It may be hard at first and you may feel more tired at the start. As with all the changes you have made, if you continue you will soon experience the benefits.

Note: Some people can't sleep at regular times each night if they do shift work or are up in the night with children. If you have children, still try and have set sleep and wake up times as much as possible. If you are being woken up a number of times during the night, try and schedule a consistent time every day to have a nap. An 'ideal' nap time would be 20-30 minutes in the early afternoon when your natural rhythm is geared towards rest anyway. If you do shift work, when you are on night duty try and have the same sleep and wake times during daylight hours.

In addition to irregular sleep patterns that affect our natural body clock, stress can also affect the way we sleep.

Sleeping too little due to stress:

Some people find that they have a hard time getting to sleep due to the stress of having a chronic illness like IBD. Stress can cause more adrenaline (a stress hormone) to be released in your body. Adrenaline tends to make you alert even when you are very tired. So, it is possible to find yourself working late into the night when you are feeling good. However afterwards you may find it difficult to get to sleep.

It is common to worry about problems related to an illness like IBD. People can also worry about the fact that they are not getting enough sleep and how this will affect them and their fatigue the next day. All this can keep you from falling back asleep and may make you feel anxious or upset.

If you find yourself waking up due to stress and worrying:

- Set a bedtime for yourself and then 'switch off' an hour before that in order to start relaxing. For example, turn off your email and mobile phone, switch your thoughts away from the children once they are in bed and turn off work related thoughts. Instead, try to do something relaxing such as reading a book, watching television or listening to music.
- Try setting a 'worry' time at least two hours before you go to bed. Write down your problems and worries that go through your head when you lie awake at night. Then write down the next step you'd like to take to resolve the problem. Be as specific as possible. It may also help to break the problem down into small parts. Once 'worry' time is done (e.g. 15 minutes) try not to allow yourself to think about your concerns anymore.
- If you can't fall asleep or you wake up because you are worrying try the following. Remind yourself that you have already written down the problem as well as the next step and that worrying is no longer going to help.
- If unhelpful thoughts come into your head, breathing exercises can also help (see below). Finish with imagining your most relaxing scene, such as lying in the warm sand on a beach or imagining a beautiful sunset.

Sleeping too much:

Some people find that due to their symptoms they sleep too much. You may hear people say that if you sleep for 12 hours it means that your body needs this amount of sleep. However, sleeping this amount every night is actually going to make you feel more tired. You will often wake up feeling un-refreshed. If you have not had enough sleep recently, having an extra long sleep can be helpful, but it should not become a habit.

If you find you are sleeping too much (more than 8-9 hours a day):

- If you go to bed early: Try going to bed a little later each night and continue to set your alarm for the same time each morning. Start-off gradually. For example, start by staying up for an extra 15 minutes, then 20 minutes the next night and so on.
- If you go to bed at a good hour but tend to sleep late: try and wake up each day a little earlier than the day before. The aim is to reduce your sleep to around 8 hours. Once again do it gradually. Start-off by waking up about 15 minutes earlier and increase this by around 5 minutes a day.
- Avoid naps during the day by sticking to your activity plan.

- At first these changes in your sleep will make you feel more tired, which can be tough. However, if you continue you will find that actually sleeping less and doing more exercise will help energise you.

Setting goals for improving sleep:

Your sleep problem may get worse before it gets better. This can make it difficult to stick to your goals. Try not to get discouraged. The long term benefits of sticking to a good sleep plan can make a big difference to how you feel and how you cope in your daily life. Remember you are retraining your body's sleep cycle. So, it may take at least a month or two before you start to feel the difference.

What factors may be contributing to issues with your sleep cycle?

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It is important to set clear weekly goals for improving your sleep and to monitor your progress. Some examples of what other people have set as their goals are:

- Go to bed at 11.00 pm and wake at 7.00 am each day of the working week.
- If I have not fallen asleep within 20 minutes, get out of bed and go read in the living room
- Even if I feel tired after a bad night's sleep I will only rest by sitting down and I will avoid napping during the day.
- What goals would you like to set for yourself?

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You may want to add this to your goal sheet for this next week.

4) Breathing

It may be hard to control the stress in your life when you have a chronic illness. Learning to relax can be an important way to feel less anxious and can help you with your sleep.

When people feel stressed or tense, they tend to over breathe by using shallow rapid breaths. This is a natural response to effort or stress. However, people who are stressed can get into a habit of over breathing all the time. This does not provide enough oxygen for everyday activities and can cause cramps, feeling uneasy, aches and pains.

Sometimes you may be breathing in this shallow way (which often makes things worse) even without realising it. The best form of breathing is called diaphragmatic breathing. This type of breathing uses the band of muscle which separates your chest from your tummy. This muscle is called the diaphragm. It is located right under your rib cage. Diaphragmatic breathing uses all of the lung volume and gives you the right level of oxygen that your muscles need in order to relax. It is an easy, quick method of reducing tension.

Try the exercise below to experience diaphragmatic breathing. It is best to sit in a gently reclining position with your head supported.

Diaphragmatic breathing:

Note: Your diaphragm is the muscle that sits below your ribs and helps to move chest wall in and out when you breathe.

Firstly, observe your normal breathing pattern for a few breaths. Then:

- Place your hand below your rib cage on your tummy. Breathe out gently.
- Now breathe in through your nose, taking the air down as far as you can into your lungs.
- When you breathe in your hand should move outwards and you should see your tummy rise up.
- Some people make the mistake of pulling their diaphragm inwards as they breathe in. This only allows the oxygen to get to the top half of the lungs, so make sure you move your diaphragm outwards when you breathe in.
- Now breathe out gently through your mouth allowing your diaphragm to move inwards.
- Focus more on the outward breath and think **RELAX** as you let it go.

- Allow all the air to leave your lungs through your mouth, but don't use any force to do this.
- After each breath pause for 1-2 seconds before breathing again

Once you have practiced diaphragmatic breathing a few times and feel that you have the hang of it, it can be done in almost any situation.

For example: sitting at your desk at work, driving your car, or lying in your bed at night. It is a useful, simple technique to use before you go into any stressful situation, or to quickly de-stress if you feel you need to.

5) Homework

We have covered a lot today. Let's review some of the homework tasks that have come out of the session:

- Practice the most helpful strategies for improving your sleep by using the goals you identified earlier and recording them on your diary for this week.
- Continue with increasing your activity levels and reducing your rest. Complete the daily diary with your achievements. Are you clear about your goals for the next week?
- Next week we will look at your own IBD symptoms. You may find it helpful to read the next section before we meet again.

Do you have any questions before we finish today?

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Session 5: Understanding your IBD Symptoms

This week we will cover:

- 1) Key points and questions from last week
- 2) Reviewing your homework: activity and rest, sleep diary, stress management
- 3) Understanding your IBD symptoms
- 4) Homework: self-monitoring your symptoms

1) Key points and questions from last week

What questions or thoughts did you have after last week's session? Let's spend a few minutes discussing them first.

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2) Reviewing the homework

Last week we asked you to continue with increasing your activity and decreasing your periods of rest. How did that go this week? Were there any problems you experienced?

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What did you achieve?

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Do you think it's useful to continue increasing activity and decreasing rest? If so, what is a reasonable goal to set for yourself over the next week?

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If you feel you have reached a helpful, consistent pattern of activity and rest, how can you try and maintain this pattern?

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You may have also set some goals related to your sleeping difficulties, and were going to keep a record of how this went.

What did you achieve?

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How has your sleep pattern been over the last 7 days?

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Did you experience any difficulties? If so, what were they?

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What is your next step in improving your sleep habits? How can you make sure you keep practicing this?

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3) Understanding your IBD symptoms: symptom focusing and symptom Attribution

Attribution means thinking that something is causing something else to happen. This week's session will focus on understanding your IBD symptoms. We know that when people focus on their symptoms and attribute a wide range of symptoms to IBD, this can actually increase their experience of fatigue.

Symptom focusing

In Session 1, we discussed that **focusing too much on your symptoms and thinking that many symptoms are a result of your IBD** can lead to feeling fatigued. It is very natural in a chronic disease such as IBD to become worried when experiencing symptoms.

This can lead to a vicious cycle because after you focus more on your symptoms you then experience more symptoms. Once you experience more symptoms, you worry more and become more anxious. Anxiety may then cause you to experience more symptoms, which can lead to feeling hopeless.

For example, you might be busy at work until you notice you have a headache. Although you have ignored it up until now, once you notice it you focus on it and the headache gets worse. Inaccurate, false thoughts and fear about symptoms can keep you from managing your symptoms in the best possible way. This can all contribute to your fatigue.

When you realise that you are focusing on symptoms, your initial response may be to try not to think about them. However, trying not to think about something often makes it worse. The more you say to yourself "I must not think about my symptoms" the harder it is to ignore them.

So what can you do about symptom focusing?

There are different strategies to reduce the amount you focus on your symptoms. The first step is to become aware of when you are 'symptom focusing'.

1. Increasing your awareness

Most people notice a change in how they are feeling (e.g. anxious) or a change in their body (e.g. more tense) when they are focusing on their symptoms. What happens when you focus on your own symptoms? How can you notice when you were doing this?

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2. Redirecting your attention

Once you have become aware that you are focusing your attention on your symptoms, you can choose to redirect your attention somewhere else. This might be a helpful strategy when you are in a situation that needs your full attention and when you don't have time to find alternative thoughts (which is the next strategy).

For example, you might be at work trying to finish a job when you feel pain in your abdomen or the need to go to the toilet. Your usual response might be to start scanning your body for other symptoms and to think it is due to IBD. Instead, you could notice that you are focusing on your symptoms, remind yourself that this is not helpful and that the symptom may go away. You can then refocus your attention on the task you were doing.

There are many different ways you can redirect your attention away from 'symptoms':

- You can focus on the sounds around you
- You can look at the pictures on the wall
- You can do some quick stretches
- You can smell your favourite soap/perfume
- You can focus on the taste of your coffee/lunch.

The main idea is to redirect your attention away from symptoms onto other things.

Symptom attribution

Thinking that a lot of symptoms are related to your illness (symptom attribution) can increase the experience of fatigue.

When you have a chronic illness like IBD it is easy to assume that all symptoms are caused by your illness. In fact, it is just as likely that common symptoms could be due to other factors such as tiredness, anxiety or the common cold.

So what can you do about symptom attribution?

Learning to manage your fatigue more effectively includes developing alternative explanations about your body sensations.

1. Developing alternative explanations

You can focus less on your symptoms by firstly; being aware of the thoughts you have about what is causing them. Then you can find alternatives to these thoughts.

For example, Nick has a thought such as “My energy level has dropped and that means I am about to have another relapse and I won’t cope”.

This may make him scan his body for other symptoms, which might suggest a relapse. This will make him even more sensitive to any changes in his body, which might have occurred anyway. Noticing all of these changes may make him more likely to think he won’t cope, which then increases his experience of fatigue.

Not all your symptoms are always related to your illness. They could be the response of your body to anxiety or depression. They could be due to a change in routine. Or they could be a symptom, which is simply part of everyday life and not a reflection of your IBD.

It may be more helpful to replace the thought, “My energy level has dropped, that means I am about to have another relapse and I won’t cope” with “I sometimes experience a drop in energy when I have been really busy, but it does not necessarily mean I am going to relapse. In fact, it is much more likely to be part of the normal variations in IBD.”

The first step in developing alternative thoughts is to understand your individual IBD symptoms as well as becoming aware of other explanations for experiencing certain symptoms. By developing these alternative explanations, you may focus less on your symptoms, and reduce your fatigue.

Alternative explanations can include:

1. Normal variations in IBD symptoms

Not everyone experiences the same symptoms and they can vary in duration and severity. A person with IBD will usually experience more than one symptom, and not everyone experiences every symptom. So, it is important that you are clear about **your individual experience of IBD**. This includes **your own** symptoms and their normal variations.

Let's take a moment to review what you believe your individual IBD symptoms are. Let's also discuss the change in symptoms you experience as part of normal variations.

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2. Symptoms related to relapse

New symptoms of relapse are usually quite easy to separate from the normal variations of IBD. They usually get worse over several days and last for a week or more. Later improvement is usually slower than the development of the initial symptoms.

Symptoms of a relapse are also individual. Focusing on these too much is usually unhelpful and may make your fatigue worse.

3. Symptoms related to medication side effects

Many people with IBD are taking medication. Some medications have side effects, especially when you first start taking them.

Because there are so many different medications, we cannot review them all. However, it is important that we know exactly what medication you are taking, how long you have been taking it, and whether you have any side effects.

What medications are you currently taking?

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When did you start taking them?

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What are the known side effects of these medications, and how long do they usually last?

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4. Symptoms related to poor routine and less activity

In Session 2, we explained that people with a chronic illness and fatigue often try to manage it by changing their routine. For example, you may try to rest more and do less activity. A consequence of this is that your body can become less used to activity. This leads to symptoms such as a poor muscle tone, difficulty exercising and more fatigue.

Symptoms related to poor routine and deconditioning are also very individual.

What do you know about your physical symptoms, which might be related to your level of rest and activity?

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5. Symptoms related to stress and anxiety

If you are stressed or anxious, you can experience reactions in your body such as fast heartbeat, muscle tension, nausea, dry mouth or sweating. Muscle tension makes it difficult for you to breathe, since there is not enough oxygen moving around your body. You may also experience physical sensations such as cramping (similar to muscle spasms), aches and pains, dizziness, pins and needles, and general uneasiness.

What physical reactions have you noticed in yourself when you get stressed or anxious?

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6. Symptoms related to depression

If you feel low in mood or depressed you may experience physical symptoms. These can include tiredness, loss of energy, problems sleeping, tension, loss of interest in sex, change in appetite (increase or decrease), problems concentrating or feeling slowed down. In turn, some of these symptoms can lead to other physical sensations. For example, if you feel depressed and eat less you may feel more fatigued.

What physical sensations have you noticed when you get depressed or low in mood?

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As you can see, there are a number of reasons for some symptoms. The aim of this session is to help you develop possible explanations for your own symptoms. This will help to reduce your symptom focusing, symptom attribution and help you in managing your fatigue.

4) Homework: Self-monitoring of symptoms

In order to start thinking about alternative explanations for your physical sensations, we would like you to keep a diary of your 'symptoms' over the next week. The **symptom diary** is on the next page and involves the following:

- Noting down physical sensations/symptoms you observe which you would normally attribute to IBD.
- Rating your stress level on a scale of 0 to 10 (0= not stressed at all, 10= highest ever)
- Rating your mood at the time on a scale of 0 to 10 (0= not at all, 10= highest ever).
- Thinking about a number of possible reasons for the physical sensation you noticed (the last three columns on the diary). We will discuss this when we review the homework next week.

Recording symptoms can sometimes result in an increase in focus on symptoms. This process can make your symptoms feel more severe than they usually do. **It is important to remember that this is because you are more focused on them, rather than because your symptoms are getting worse.** If you like, we can fill out one example together.

Do you have any questions before we finish today?

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Session 6: Changing Your Thinking

This week we will cover:

- 1) Key points and questions from last week
- 2) Reviewing your homework: the symptom diary
- 3) Identifying unhelpful thinking
- 4) Developing alternative thoughts
- 5) Homework for next session

1) Key points and questions from last week

What questions or thoughts did you have after last week's session? Let us spend a few minutes discussing them first.

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2) Homework review

Let us have a look at the symptom diary you completed over the last week:
What have you noticed about your symptoms?

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Were you able to find alternative explanations for your symptoms? If so, did this change the way you felt?

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What are some possible explanations for your symptoms?

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When you look back, which explanations seem to be the most helpful to you?

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What have you learned from this exercise? How could you continue to reduce your symptom focusing and attributions?

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3) Identifying unhelpful thinking

In an earlier session, we introduced the five-part model of fatigue. We also explained that the way we think can impact how we feel, act and how we manage fatigue. However, we are sometimes unaware of our thoughts and the impact that they can have on us. We have also discussed how some thoughts can be more helpful or less helpful in understanding your IBD symptoms.

In today's session we will help you identify thoughts that may be unhelpful in managing your symptoms and fatigue. Negative thoughts might make you feel unhappy or distressed. They may also prevent you from managing your symptoms in the best possible way. Together we will find ways for you to develop more helpful thoughts to better manage your fatigue.

All of us have negative or unhelpful thoughts that we are unaware of at times. This is because negative thinking is usually automatic. We are often more aware of how we are feeling rather than the thoughts that lie beneath these feelings. For example, if you are at a party and begin to feel fatigued, you may become aware of the feeling of panic and the need to go home. You may be less aware of the thoughts going on in your head. These could be: *"I am beginning to feel tired, I have to go home immediately. If I don't, I might have a relapse."*

The first step in managing your thoughts is to identify negative thoughts. Once you can identify your thoughts, you can start to examine them, and then look for more helpful alternatives. Helpful alternatives do not necessarily have to be positive thoughts. They may just be more realistic ways of viewing the situation.

It is important to realise that there is no 'right' or 'wrong' way of thinking. Everyone has negative thoughts from time to time. However, some thoughts are not as logical, as we think they are. Learning to recognise some of these unhelpful patterns in your own thinking can be an important step towards better managing your symptoms.

Common unhelpful thoughts

Here are some common unhelpful thoughts that people with IBD have identified:

1. I am afraid I will make my symptoms worse if I exercise.
2. The severity of my symptoms must mean there is something serious going on in my body.
3. Symptoms signal that I have overdone it.
4. If I push myself too hard I will relapse.
5. I can't cope with this.
6. My illness is awful and my symptoms are completely unpredictable and uncontrollable.
7. This pain is going to keep me up all night.
8. People must think, I am really strange, because I'm always turning down invitations.
9. I should pay close attention to how well or how badly I am feeling.
10. People will think badly of me because of my symptoms.
11. I might not be able to get to the toilet in time when I need it.

Are any of these familiar to you? In the following sections, we look at some of the common errors that underlie thoughts such as these. See if you recognise some of these in your own ways of thinking.

Common negative thinking

(i) Shoulds:

Examples

"I should be able to cope with my IBD symptoms better"

"I should be able to complete all these tasks like I used to"

Many thoughts include the word 'should'. The word 'should' suggests that there is a standard or fixed rule that must be followed. We can apply this way of thinking to ourselves or to others. For example, we may feel that others 'should' act in a certain way all the time. We may also spend quite a lot of time telling ourselves how we 'should' be acting.

This can lead to difficulties as it fills us with expectations of others and ourselves that are: 1) probably not possible and 2) leave us feeling disappointed or upset.

The problem with 'should' thoughts is that they are often not possible in reality. So they leave us upset when things do not go as we wanted them to go.

(ii) Black and white thinking:

Examples

"I will never be able to exercise again"

"My IBD symptoms are completely unpredictable and uncontrollable"

The tendency to think in 'black and white' or in absolutes is another common issue. These thoughts often contain a never or always statement. As IBD is an on-going problem it is not uncommon for people to think about their illness in terms of "*always having it*" or "*never managing my symptoms*".

Other examples may come-up in your day-to-day life. You may think, "*I am never on time*". However, chances are that you will be on time, at least some of the time! You may have thoughts such as "*I always mess things up*". This type of thought is not only highly unlikely; there are also few absolutes in the world. So using 'never' or 'always' is usually unhelpful.

We may also have these thoughts about other people such as "*she never thinks about how I might be feeling*". Realistically, 'never' and 'always' are rarely true when thinking about others or ourselves.

(iii) Catastrophising

Examples

"I am going to overdo things and have a complete relapse"

"Being fatigued is the worst feeling in the world"

"If I have another relapse I will end up in hospital"

"If I go out, I will be totally embarrassed by my symptoms"

As you can see from the list of examples, catastrophising is a common error. This is the tendency to think the worst about situations. People who catastrophise tend to think about things in an unbalanced way. This often leads to feelings of anxiety, panic or distress. For instance, Sally starts to worry when her husband is five minutes late from work. She is convinced that he has been in a terrible accident. When he arrives home safely thirty minutes later, she has already made herself feel sick with worry.

People who catastrophise often jump to conclusions about future events and imagine the worst possible outcome. For example, John has been told that he will be fine on medication and will not need an operation for his IBD. However, he thinks that the doctor did not want to worry him at the time of being diagnosed, so he begins to worry.

(iv) Over generalising

Examples

"The last time I did too much it set off my fatigue, so I better not ever overdo things"

"Oh no, I've started to have more frequent stools. It's bound to get worse like the last time and I will have a major relapse"

When we over generalise, we come to conclusions based on one experience or aspect of a situation. For example, Joan thinks, "I've tried changing my daily routine this week and since it did not make any difference, there is no point because it will never work".

(v) Predicting the future

Examples

"I just know that if I keep up my exercise routine it will cause a relapse of my symptoms."
"I will end up incontinent or house bound"

Without realising it, many of us have negative thoughts about future events. If we think, we are going to feel bad we often end up feeling that way. However, none of us can really predict what is going to happen in the future.

(vi) Eliminating the positive

Examples

"I feel good today, but I usually have so many symptoms. It won't last"

It is often easy to dwell on aspects of our bad experiences and to ignore or forget about the good ones. For instance, Jeremy's boss gives him some feedback about his work. Most of this is very positive. However, he also tells Jeremy that he needs to be a bit more assertive in meetings. Jeremy goes home thinking that he is doing a terrible job. In this situation, Jeremy has ignored the fact that most of the feedback was positive and has only focused on the negative.

(vii) Mind reading

Examples

"People must think I am really strange because of frequent trips to the toilet"
"I am sure my partner thinks that I am exaggerating and that my loss of energy is all in my head"

We constantly make assumptions about what others are thinking about us. These assumptions are usually negative; such as "Because my house is a mess, they must think I am a lazy housekeeper." However most people are more worried about the impression they are making on you to have time to make judgments. Some people are very critical, but it is worth thinking about whether these people's opinions need to matter that much to us.

(viii) Negative thoughts related to perfectionism

Examples

“Even though I am feeling really tired I need to get the house spotless before the visitors arrive”

“I can’t have a little nap because it means I am not a good parent”

Perfectionism is the tendency to set very high, inflexible standards for yourself, your performance or your achievements. This can be helpful in terms of producing good results and keeping other people happy. However, it can also result in feeling unhappy because things are not of a high enough standard. Perfectionism can lead to negative thoughts, and these can make you more stressed with more negative emotions. This makes it difficult to manage fatigue since negative emotions and stress often cause fatigue.

Recording your negative thoughts

We would like you to use the thought record at the end of this session to record your daily negative thoughts as soon as they happen (negative thought column on the thought record). Your thoughts can be related to your IBD, your fatigue or to other daily events in your life. They will usually be accompanied by a strong emotion. In addition to the negative thought, write down exactly what you were doing when the thought occurred (situation column).

We also ask you to record how you were feeling at the time (feeling column). In fact, the times where you feel a very strong emotion are usually the times where you are likely to have unhelpful negative thoughts. Recording your feelings can help you make the link between your emotions and thoughts. It can also be quite hard to access your negative thoughts if you are not used to doing this. When you become aware of a negative feeling, if you are then finding it difficult to work out what you are thinking, write this feeling down first. Then, spend a moment working out what the thought is that underlies this feeling.

At the start it may feel a bit strange writing your thoughts down. You may worry that you will make them worse by focusing on them, or you may feel that they are silly. Remember – no thought is too small to write down – you need to know what your thoughts are before you can manage them.

The table on this page shows you an example of a thought record written by a person with IBD. We have added in the unhelpful aspects related to each of the thoughts. Have a look through these examples and then spend the next few days filling in your own thought record.

Each day you may like to go back at the list of common issues in thinking and see if you can identify your own unhelpful thoughts. Once you feel that you can easily identify your thoughts, move on to the next section. This part gets you to challenge your negative thoughts and come up with alternative ways to look at the situation (alternative thought column).

Date	Situation (what I was doing)	Feeling	Negative thought (What I was thinking (in detail))
14 May	About to go out for dinner with a friend	Anxious	There is no way I can go out with this fatigue. I will never enjoy myself. (black & white, predicting the future)
15 May	Talking with mother on phone about my difficulties coping with IBD	Angry Frustrated	She doesn't understand me at all. She should listen to me when I try to explain my IBD. (black & white, should)
16 May	Trying to get the children ready for school and not having the energy	Distressed	Here we go again. I am going to spend the whole day feeling unwell and tired and this is the first sign of a relapse. (catastrophising, predicting the future)
17 May	Sitting in a meeting at work and having the feeling as if I can't remember things and I can't find the right words'	Anxious Embarrassed	This is a nightmare. What if I someone notices? They will think I am strange and avoiding the meeting. (catastrophising, mind reading)
18 May	Handing in report at work	Distressed	I know my boss is going to think it's useless. I would have liked to have spent at least another day perfecting it. (perfectionist thoughts)

4) Developing alternative thoughts

Once you have identified your patterns of negative thinking, the next step is to evaluate your thoughts and to look for more helpful alternatives. This is the last column on your thought record (Thought Record for Session 6).

Weighing up the evidence

There are many different ways to look at any situation. More often than not, an unhelpful thought ignores some of the key facts. Once you have identified a negative thought you can spend a bit more time looking at the evidence for your thought.

These are some questions to ask yourself when weighing up the evidence:

1. How else could I interpret what has happened?
2. Do some of the facts contradict what I am thinking?
3. Am I just focusing on the negative aspect of the situation?
4. Am I seeing the picture in black and white?
5. Am I expecting the worst (catastrophising)?
6. What is truly the worst thing that can happen in this situation?
7. Am I trying to predict the future or read other people's minds?
8. Am I jumping to conclusions based on a previous experience?

You will probably find that some of your unhelpful thoughts have evidence for and against them. By looking for evidence, you are less likely to have completely negative thoughts. This will help you break the habit of automatically focusing on the negative.

Coming up with alternatives does not mean you have to be positive all the time. It simply means there are other ways of viewing the situation, which may be more balanced and more helpful to you.

Coming up with alternatives

At first, it may be hard to identify helpful alternative thoughts. You may have some negative thoughts that are overwhelming. The best way to challenge your thoughts is to list all the evidence for and against your negative thought. You can then review the evidence for and against, assess how accurate your original thought was, and then develop an alternative more helpful thought.

Remember, thoughts are neither true nor false. It is a matter of looking at the logic and the evidence linked to them. You may find it hard to be convinced by your alternative thoughts at first – but do not give up. Negative thoughts are like any bad habit, they are hard to change and we all need to keep working on them.

We are often better at giving good advice to others than ourselves. One way to help yourself with alternative thoughts is to imagine you are giving advice to a good friend who is upset with their negative thinking.

Just as negative thoughts can become automatic, challenging those thoughts can also become automatic. The goal of this exercise is to help you be able to automatically challenge your negative thoughts.

We have given you some possible alternatives to the thought record we showed you earlier. Once you have read these, try making-up alternative thoughts for the negative thoughts you wrote in your daily record. Then, for the rest of the week, try to record your negative thoughts as they occur. Finally, write your alternative thoughts on the other side of the sheet.

Once you feel you have a good understanding of this exercise, go back to your thought record and rate how strongly you believe each of your thoughts to be true (both your negative and alternate thoughts). Give them a rating out of 100.

At first, you may find that you rate your negative thoughts higher than your alternate thoughts. Over time though, this should change and you will become more convinced by the alternatives. You can continue this exercise for the rest of the programme by continuing to fill in the 'alternative thought records'. More of these can be found at the end of each remaining session.

Date	Situation (what I was doing)	Feeling	Negative thought (What I was thinking (in detail))	Alternative thought
14 May	About to go out for dinner with a friend	Anxious	There is no way I can go out with this fatigue. I will never enjoy myself. (black & white, predicting the future)	If I don't focus on the fatigue, it may not seem so bad and I might enjoy myself more.
15 May	Talking with mother on phone about my difficulties coping with IBD	Angry Frustrated	She doesn't understand me at all. She should listen to me when I try to explain my IBD. (black & white, shoulds)	She doesn't understand my IBD but that doesn't mean she doesn't understand me at all. She does listen to other problems.
16 May	Trying to get the children ready for school and not having the energy	Distressed	Here we go again. I am going to spend the whole day feeling unwell and tired and this is the first sign of a relapse. (catastrophising, predicting the future)	I am going to stick to my planned routine and do some exercise. This way I may help to manage my fatigue and there are lots of other explanations for feeling fatigued.
17 May	Sitting in a meeting at work, not being able to concentrate and not remembering words	Anxious	This is a nightmare. What if someone notices? (catastrophising, mind reading)	The worst thing that can happen is they think I drank too much coffee.
18 May	Handed in report to boss	Distressed	I know she is going to think it's useless. I would have liked to have spent at least another day perfecting it. (perfectionist thoughts)	There is never enough time to do things as perfectly as I would like. She has always been happy with my work in the past and if she wants me to change something it is easy to do it.

Just as negative thoughts can become automatic, challenging those thoughts can also become automatic. The goal of this exercise is to help you be able to automatically challenge your negative thoughts.

We have given you some possible alternatives to the thought record we showed you earlier. Once you have read these, try making-up alternative thoughts for the negative thoughts you wrote in your daily record. Then, for the rest of the week, try to record your negative thoughts as they occur. Finally, write your alternative thoughts on the other side of the sheet.

We have covered a lot of material about identifying and changing unhelpful thoughts. Before we talk about your homework tasks, would it be useful to fill out a thought record together using one of your own thoughts?

5) Homework

Tasks for this week are:

During the next week, we would like you to complete the thought record every time you notice a change in mood. Try identifying any unhelpful thoughts, and then develop an alternative thought.

Next week we will introduce a section on stress and determining a sense of control. You may find it helpful to read those sections in your manual.

We will discuss the thought record again at the beginning of next week. If you have any difficulties or questions we can review it then.

Do you have any questions before we finish today?

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Session 7: Managing stress, developing a sense of control and coping with emotions

This week we will cover:

- 1) Key points and questions from last week
- 2) Reviewing your homework: thought records
- 3) Managing stress and having a sense of control
- 4) Coping with emotions
- 5) Homework for next session

1) Key points and questions from last week

Last week we discussed the idea of changing unhelpful thinking.

Do you have any thoughts or questions or after last week's session? Let's spend a few minutes discussing these first.

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2) Reviewing the homework: thought records

Let's review the thought record you completed last week. What was it like to record your negative thoughts? What did you learn from doing this task?

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How easy was it to develop alternative thoughts? What did you notice about your mood?

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How might changing your thinking in this way help manage your fatigue?

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3) Managing stress and the influence of your thinking

As we have said before, people with IBD have to cope with a great deal of stress. This can affect your sleep and make you feel more fatigued. It may also mean that when you have less energy you try and do things for others, leaving little time left for yourself.

Stress can cause a response from your body known as the 'fight or flight' response. It causes your central nervous system to become more active. Stress hormones, such as adrenaline are released and your heart starts pumping faster to supply blood to large muscle groups. Your breathing also becomes faster in order to supply more oxygen to your muscles. Over time, on-going stress can result in physical fatigue. Similarly, constant mental overload due to stress can lead to mental fatigue.

The session today will focus on **the influence of stress on fatigue**. Being tired can make you feel more stressed and less able to cope. Feeling stressed can then make you feel more fatigued. Below we provide some tips for reducing the impact that stress has on your life. We also discuss ways of managing controllable and uncontrollable stressors.

General tips to reduce the impact stress has on your life

Changing your thinking:

Our daily activities are often 'framed' by our thoughts and feelings. Sometimes these are unhelpful which adds to the stressful impact of the event. Changing your thinking from unhelpful negative thoughts to a more balanced perspective can help manage your stress. The case of Sue is a good example of this.

Example:

Sue finds that by taking an hour walk in the park she feels much better. She is able to relax and feel more positive about her problems. However, she also feels she is letting her family down by not getting practical errands done during this time. The good feeling is reduced by her feelings of guilt for taking this time out of her busy schedule.

Sue learns how to think differently about this time out. She tells herself that she will have more energy for the people and practical things in her life if she takes time out to relax and exercise. She replaces the idea of letting her family down with a new thought of the importance of 'self-care'.

Try thinking of something that you could give new meaning to in your life. Feel free to write it down in the space provided:

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Learning how to say “no”:

In an earlier session, we discussed the importance of developing a consistent pattern of activity, rest and sleep in order to help you manage your fatigue better. This change in routine may at times make it difficult to respond to all the requests of others.

Learning how to say no to commitments or to other people can be difficult. It is important to realise that saying no is not a failure. Especially when it helps you become healthier and more capable of doing the things that you want or need to do. We are all entitled to say no and it doesn't mean that we are rejecting the person who is asking. .

Prioritising:

Part of saying no to some things or people is becoming aware of your needs and priorities. By saying no to certain people and things in your life, you can then say yes to the most important aspects in your life.

While priorities are often shaped by your responsibilities to family and work, it is also important to realise the importance of self-care. It is time well spent, prioritising the things you enjoy, or exercising, which both help you to relax. .

Looking after yourself:

By looking after yourself and making your health a priority, you will have more energy and time for others in the long run. It may seem that you don't have time for activities that will help you to cope and relax. However, by making some time available each day for yourself and your health, you will have more quality time overall.

Reward yourself with something you enjoy:

Stress happens. We all have some episodes in our lives that are difficult, tragic, painful or frustrating. It is important during those times to focus on something that is pleasurable or beneficial to your sense of wellbeing.

People who feel stressed usually say that they have no time to do enjoyable things. Make it a priority to take time to do the small things that you enjoy, particularly when you are stressed. These may just be simple things such as walking through a park, curling up with a good book, reading the newspaper, catching up with close friends, taking a hot bath, or just simply putting your feet up.

You may like to experiment with one or more of these strategies to reduce the effects of stress.

Managing controllable and uncontrollable stressors

Research has shown that when we increase our sense of control over stressful events, we lower our stress levels. You may have noticed that when you think that you can cope with a difficult event, it doesn't seem as stressful. You also may know people who live with a lot of stressful demands on them, but they don't seem to be stressed. This may be due to their sense of control over the demands on them.

Determining control:

As part of having IBD, you will have found that there are some things you have control over, and other aspects that you don't. There are different ways of **managing controllable and uncontrollable stressors** which impact on your fatigue:

1. Controllable stressors:

Controllable stressors are things related to your illness or other aspects of your life, which can be dealt with or changed in some way. Sometimes it seems easier to avoid dealing with a difficult situation by allowing the situation to continue because it feels too hard to change. While this may work in the short term, in the long term it may also make you feel helpless.

Controllable stressors can be best-managed using strategies, which may change the situation in some way. For example:

- Finding ways to avoid excessive use of energy, without avoiding activity.
- Saying no when there are too many demands on you.
- Telling people how you feel when you are overwhelmed with emotion.

Research has shown that for many people it is the every day small hassles that get them down. Quite often, these can be handled differently with some thought or planning.

The key to finding control in these situations is to break the problem down into smaller parts. For example, you may feel stressed about your situation at work. It may at first seem impossible to change your work environment. However, you may be able to change the way you think about your work or the way you respond to your work environment. You could also change the way you communicate with people at work.

You may be able to make simple changes. For example: making sure that you take half an hour for lunch or by letting people know that you have IBD (which can get in the way of your performance at times).

Can you think of some ways you have already taken control over controllable IBD stressors?

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Can you think of other areas where you could gain control, but haven't?

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2. Uncontrollable stressors:

Uncontrollable stressors are those aspects of your illness or situation, which you don't have control over. Trying too hard to gain control over uncontrollable aspects of your illness can lead to more fatigue.

Uncontrollable stressors are best managed with strategies such as getting social or emotional support. It can also help by looking at the situation in a more helpful way.

For example, it is very difficult to predict how your illness may progress and when you might have another relapse. This can be scary and difficult. However, one way to deal with this uncontrollable aspect is to talk with close family or friends about this. Expressing your fears or other feelings can help you accept what is uncontrollable. It is okay to let people know that you are feeling afraid or vulnerable at times. It is also okay to ask for support when you need it. We will talk more about this in the next section.

Another tip is to identify whether you are thinking in a balanced and helpful way. This is similar to what you did in your thought records in the last session. It might be the case that you are telling yourself that your life will be awful and that you won't cope (catastrophising). This is not necessarily the case, and it is important for you to develop more helpful ways of thinking about the situation. Remember that you can use thought records for this.

Are there any aspects of your situation that you experience as uncontrollable? What are they?

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Can you think of some ways you could manage these in a more helpful way?

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4) Coping with emotions

At the start of this manual we introduced you to a model for explaining IBD-fatigue. This included an emotion component.

It is normal, for people who have a chronic, unpredictable disease like IBD to experience a range of emotions. These may include sadness, grief, frustration, anger, depression, fear, anxiety, embarrassment and shame. These feelings are common in most chronic illnesses, and can have an impact on your symptoms.

Feeling tense, stressed, anxious or low in mood is unpleasant enough. However, these feelings can also produce changes in your body. These include more fatigue, muscle pain, problems with memory, poor concentration, less activity and low motivation. These symptoms can then overlap, worsen and prolong IBD-fatigue.

Strong emotions are a signal that something important is going on in your life. Identifying specific moods can help you choose certain strategies to improve or reduce the strength of these moods. Ignoring or pushing away your emotions may not be helpful in the long term, both in terms of your IBD symptoms and your fatigue.

Do you often experience negative moods? If so, what are they?

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How have you coped with feelings like these in the past? What has been helpful? What has been less helpful?

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There are different strategies that can be helpful for managing different feelings. We will introduce these here today. You will probably find that some of these strategies have already been covered during the last seven weeks:

Feelings of sadness, grief and loss

It makes sense for a person who has IBD to experience times of sadness and grief. This is a sign that you are adjusting to changes and loss. Helpful strategies to use when you feel this way include:

1. getting support from family and friends
2. telling people how you feel
3. balancing the need to adjust to changes with doing nice things for yourself
4. borrowing self-help books from the library

Feelings of frustration or anger

Feeling angry and frustrated can be a common experience with any chronic illness because people have to adjust to limitations linked to the symptoms of their illness. For example, you may no longer be able to attend as many after work activities as before. This can result in you feeling frustrated or angry.

Ways to manage these feelings can include:

1. doing physical exercise to 'let off steam'
2. talking to people
3. using thought records if unhelpful thinking contributes to your anger
4. expressing anger in a non-aggressive manner
5. finding alternative ways of getting some of your needs met

Depression

Depression and low mood is a common feeling in people who have IBD, and can interfere with work or personal relationships. Things that can help when you feel depressed include:

1. scheduling fun activities or ones that allow you to accomplish something
2. improving personal relationships
3. medication (in some cases)
4. changing unhelpful thoughts like you did in Session 6

Fear and Anxiety

Given the unpredictable nature of a chronic illness like IBD, fear and anxiety are common emotions. When you experience severe and unpredictable symptoms by doing an activity, you may end-up feeling anxious before any task. This is due to the fear of not being able to complete it without any negative effects. Similarly, you might feel anxious because you believe you should be doing more, are letting other people down, or other people might expect you to function better.

You can manage these moods by:

1. using relaxation techniques such as controlled breathing
2. identifying and changing unhelpful thinking (e.g. catastrophising)
3. learning to cope with situations where we feel anxious (and not to avoid them)
4. Sometimes just letting people know that you are anxious can also help.

Embarrassment and Shame

People can experience embarrassment and shame about their IBD symptoms. Overcoming these feelings can include:

1. telling others about how you feel and getting their support
2. changing any unhelpful thinking that contributes to your feelings (e.g. mind reading)
3. learning to cope with the situations where you feel embarrassed or ashamed (and not to avoid them)

Which of these emotional coping strategies would you like to experiment?

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Feel free to add these to your goal sheet for this week.

Hopefully, some of the tips for managing stress and coping with emotions will help you gain a sense of control over your tension levels, your sleep patterns and your daily stresses. Remember, making changes to your routine can make your symptoms feel worse as your body takes time to get used to something new. So, be gentle with yourself and remember that you can't do everything at once. You may like to start out by trying one or two of the suggestions. As things improve you will feel able to make more changes.

Although we have set this up as an 8-week programme, in many ways the changes you have made are just the beginning. We encourage you to keep working on your goals and making new ones as you progress.

5) Homework:

We have covered a number of strategies to help you manage stress and to develop a greater sense of control linked to your symptoms and personal situation. Which of the strategies discussed would you like to try? You may want to record them on your goal sheet for this week. A copy can be found at the end of this session (Session 7).

From the 'coping with emotions' section, you may have chosen some new strategies to experiment with on your goal sheet.. This may include using the thought record (on the last page of this session) to continue to identify and change unhelpful beliefs that contribute to strong negative emotions.

Do you have any questions before we finish today?

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Session 8: Social Support and Preparing for the Future

This week we will cover:

- 1) Key points and questions from last week
- 2) Reviewing your homework
- 3) Social support
- 4) Preparing for the future
- 5) Feedback

1) Key points and questions from last week

Last week we discussed the concept of stress, developing a sense of control and coping with emotions.

What thoughts or questions did you have after last week's session? Let's spend a few minutes discussing them first.

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2) Homework review

Last week you worked on your goal sheet for managing stress, developing a sense of control and coping with emotions. How was that?

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What did you find helpful in terms of managing these aspects differently?

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You may also have completed another thought record. What did you find from doing this?

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Was there anything else from your homework tasks you would like to talk about?

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3) Social support

In the previous section, we talked about the importance of having supportive people around you, who you can talk to. With a chronic illness like IBD, and its associated fatigue, it is even more important for you to gain support from your relationships.

In order to make the best use of your supports and relationships it is important to know **who can offer what type of support**.

Not every person can offer you the same support. For example, you might find that when it comes to finding practical solutions a certain friend might be the most useful. Whereas if you wanted to talk about how you were feeling, your best friend or partner may offer better support. In fact, it is helpful to share the support amongst your friends, family and professionals. This way you don't have to rely on just one person.

Below is a table for you to write down who you have in your life that supports you, and what type of support they are good at giving. Types of support can include:

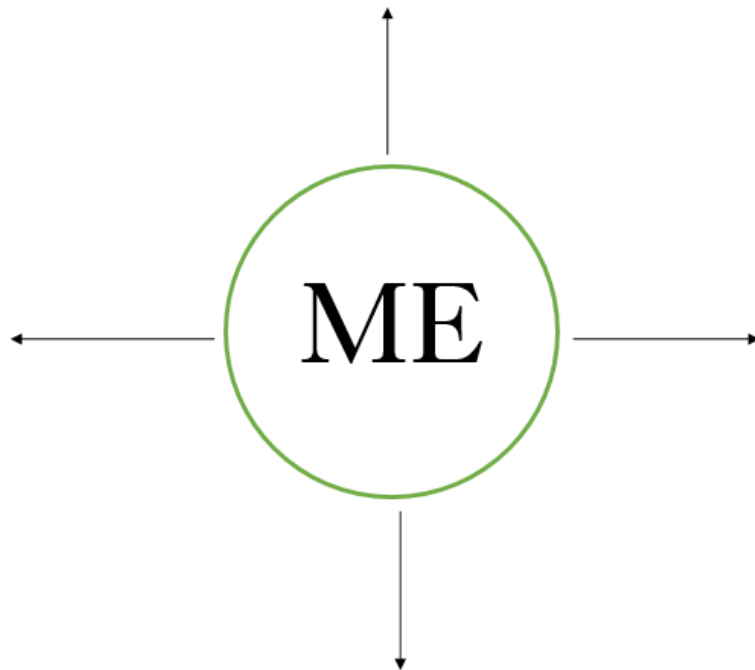
- **Emotional support** from people you can talk to about your feelings
- **Practical support** from people who can do tasks for you like shopping or gardening
- **Informational support** from people who can give you practical information about your symptoms or illness

My Support Network

Persons Name	What support are they likely to be good at?
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	

You may choose to write or draw your support people in the diagram.

My Support Network:



Is there anyone who you have not asked, but would offer you support? Who are they and what kind of support could they offer? What has stopped you from asking them and what would it take to ask them?

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When stress is high people need their sources of support the most. So, it is in our own interest to also think about **how to look after our support people**. It may be important to let off steam in ways that don't run the risk of upsetting others and damaging relationships. For example, it is better to go for a walk rather than getting into an argument. It is also helpful to continue to do things you enjoy with the people around you and to return the support when it is needed. This will help keep your relationships healthy and balanced.

In what ways do you already give to your relationships? Can you think of any other ways you can give back to your social supports?

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Are there any ways you could improve your support network? If so, what action(s) would you like to take?

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4) Preparing for the future

Eight sessions is a short time to make major changes in your behaviour or the way you think and feel. There are specific moments where you may be more at risk of a setback in fatigue. For example, a relapse in your IBD, stressful life events (e.g. changing job, someone dying, moving house), or depression can make you more vulnerable. This is because all of these events can increase fatigue, or limit your ability to continue regular, planned activity. Experiencing these stressful events does not mean that you will automatically have a setback. It simply means that these are times when you are more at risk.

During these times, it is a good idea to look after yourself by making sure that you use your helpful stress management techniques. It may even be worth re-starting a small programme of planned activity and rest. This can be a positive way to minimise any setbacks to managing your fatigue.

You may also be at risk of slipping back if:

- You simply stop using the techniques used in treatment;
- you do too much activity;
- you do not do enough activity.

This can be avoided by remembering the ideas of consistency and moderation.

Summary of strategies:

It is important that we review the strategies you have learned and discuss ways you can continue your progress in managing your fatigue. One way to maintain the changes you have made is for you to summarise and record what has been useful from each session. Let's spend a few minutes reviewing what you have learned in the last eight weeks:

Week 1	
Week 2	
Week 3	
Week 4	
Week 5	
Week 6	
Week 7	
Week 8	

Sustaining and building upon improvements

You have now practiced many activities several times a day as part of your treatment programme. These are most likely done automatically by now.

In order to maintain the gains you have made, it is important to make sure that the positive steps you have taken in treatment are now part of your daily life or you risk sliding back.

Other ways you can sustain and build on your progress are:

- Be sure to keep a sensible balance. Balance your days between different kinds of activity and relaxation.
- Continue to work on the things that you find difficult (ex. unhelpful thoughts). Remember to do this regularly and gradually.
- Continue to set yourself weekly targets. Break them down into manageable chunks and practice them regularly.
- Keeping a diary of any remaining goals or tasks until you can achieve them consistently, without feeling too tired.

How would you like to continue to sustain and build upon the progress you have made regarding your fatigue?

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5) Feedback

As we said earlier, many people continue to make improvements after treatment ends so, we would like to follow up with you at different points during the next 12 months. This helps us evaluate how useful the treatment has been. We will contact you in about 3 months for the first follow-up, then again in 6 and 12-months' time.

Before we finish our last session, we would really like to hear any feedback you would like to give about the programme:

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We would also like to ask you to comment on what you think had the biggest impact in terms of improving your fatigue.

On a scale of 1 to 10 (1= not helpful and 10= very helpful) how would you rate each of the eight sessions?

Session 1: IBD-Fatigue Explained =

Session 2: CBT for IBD-Fatigue =

Session 3: Activity Scheduling =

Session 4: Improving your Sleep =

Session 5: Understanding your IBD Symptoms =

Session 6: Changing your Thinking =

Session 7: Managing Stress =

Session 8: Social Support and Preparing for the Future =

**Thank you very much for participating in this research project.
Good luck in the future!**

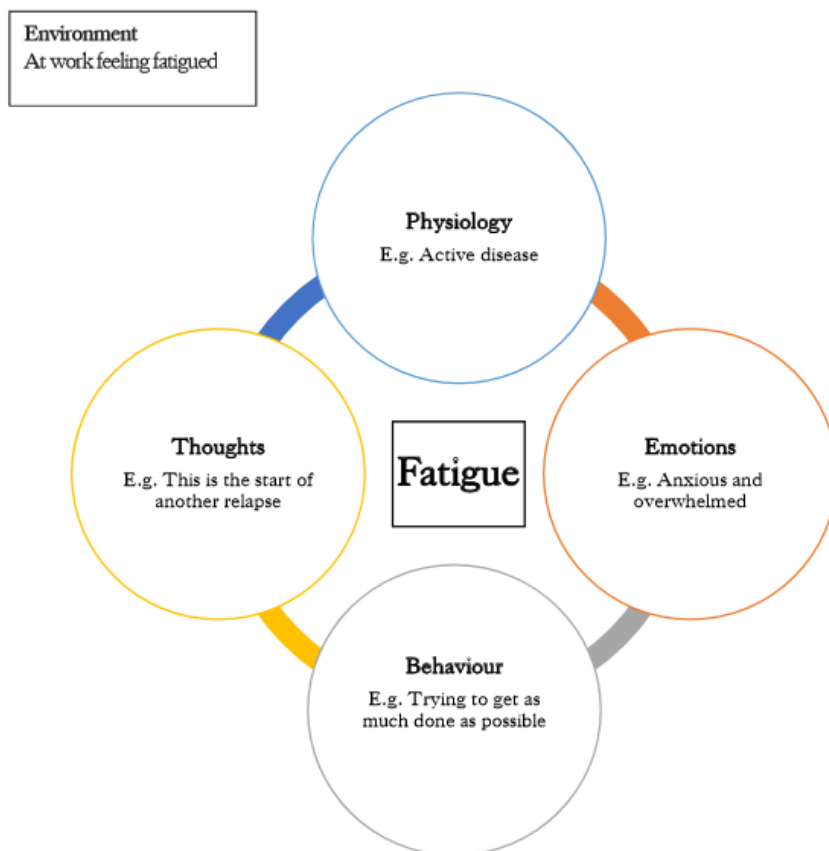
Patient ID:

A Model for IBD-fatigue

Session 1

Using the model diagram

Instructions: The following activity will help us understand what happens when you get fatigued. Please fill in the blank model (below) using your own personal examples of behaviours, thoughts, feelings and environmental factors.



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Patient ID:

Self Monitoring Dairy

Session 2

Instructions: Using the scale from 0 to 10 (not at all - to severe). Please write down your fatigue severity for each day. Remember to include what activity you were doing.

Fatigue:

^ ^ ^ ^ ^ ^ ^ ^ ^ ^

0 1 2 3 4 5 6 7 8 9 10

None **Mild** **Moderate** **Severe**

	MON	TUES	WED	THURS	FRI	SAT	SUN
Wake up time							
Morning							
Fatigue							
Midday							
Fatigue							
Afternoon							
Fatigue							
Evening							
Fatigue							
Bedtime							

Patient ID:

Activity and Rest Goal Sheet

Session 3

Write your goals in the column provided for each section. If a section does not apply to you, leave it out. In the columns marked Monday-Sunday place a tick if you achieved the goals or a cross if you did not manage to meet your target. If a goal is set for only a few days a week, leave the other days blank and tick or cross on the chosen days(s).

Activity Goals:

Goals:	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
1.							
2.							
3.							
4.							

Resting Goals:

Goals:	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
1.							
2.							
3.							
4.							

Patient ID:

Sleep, Activity and Rest Goal Sheet

Session 4

Write your goals in the column provided for each section. If a section does not apply to you, leave it out. In the columns marked Monday-Sunday place a tick if you achieved the goals or a cross if you did not manage to meet your target. If a goal is set for only a few days a week, leave the other days blank and tick or cross on the chosen days(s).

Sleep Goals:

Goals:	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
1.							
2.							
3.							
4.							

Activity Goals:

Goals:	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
1.							
2.							
3.							
4.							

Resting Goals:

Goals:	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
1.							
2.							
3.							
4.							

Patient ID:

Self-Monitoring Diary for Physical Symptoms and Sensations

Session 5

	Physical sensation(s)	Stress Rating (0-10)	Mood, Rating (0-10)	Possible reason 1	Possible reason 2	Possible reason 3
Mon						
Tues						
Wed						
Thurs						
Fri						
Sat						
Sun						

Remember to keep-up with your exercise and to sleep as well! Extra Sleep, Activity, Rest Goal sheets provided at the end.

Patient ID:

Thought Record

Session 6

Date	Situation (what I was doing)	Feeling	Negative thought (What I was thinking (in detail))	Alternative thought

Date	Situation (what I was doing)	Feeling	Negative thought (What I was thinking (in detail))	Alternative thought

Patient ID:

Goal Sheet: Managing Stress, Creating a Sense of Control and Coping with Emotions

Session 7

Write your goals in the column provided for each section. If a section does not apply to you, leave it out. In the columns marked Monday-Sunday place a tick if you achieved the goals or place a cross if you did not manage to meet your target. If a goal is set for only a few days a week, leave the other days blank and tick or cross on the chosen days(s).

Managing stress and determining a sense of control

Goals:	Mon	Tue	Wed	Thu	Fri	Sat	Sun
1.							
2.							
3.							
4.							

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Coping with emotions

Goals:	Mon	Tue	Wed	Thu	Fri	Sat	Sun
1.							
2.							
3.							
4.							

Patient ID:

Thought Record

Session 7

Date	Situation <i>What was I doing?</i>	Feeling	Negative Thought <i>What was I thinking?</i>	Alternative Thought

Patient ID:

Thought Record

Session 8

Date	Situation <i>What was I doing?</i>	Feeling	Negative Thought <i>What was I thinking?</i>	Alternative Thought

Appendix XII: Pilot RCT Patient Information Sheet



PARTICIPANT INFORMATION SHEET: RCT and INTERVIEWS

Study Title: MODIFY Fatigue

IRAS Number 212340

Version 1.4. Date: 17-11-2016

Chief Investigator: Professor Christine Norton, King's College London
Principal Investigator: Julie Duncan, IBD Clinical Nurse Specialist, Guy's & St Thomas' Hospitals

Managing fatigue in people with inflammatory bowel disease (IBD)

Fatigue has been defined as an overwhelming sense of tiredness, weakness or exhaustion, which can be mental, physical, or both. A team of researchers including academics at King's College London are conducting a study to determine whether treatments be known to be helpful in treating fatigue in other long-term conditions can also help people with IBD. This information sheet explains the study, in which we will deliver two different types of care to see which works best for people with IBD-fatigue, and interview some participants about their experiences. We would like to invite you to take part. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with family, friends or your care team if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

What does the research aim to do and what are the benefits?

We know from our clinical experience and from previous research we have done, that many people with IBD suffer from fatigue, but often do not receive help to manage this. Fatigue is one of the most common symptoms in patients with IBD and it can impact on people's quality of life. We also know that many people still suffer from fatigue when they have no other bowel symptoms and it is not necessarily linked to relapse.

There are interventions which have been shown to be effective for people with fatigue who have other long-term conditions, but these have not been tried in people with IBD-fatigue. We want to try these interventions to see which ones, if any, work best for people with IBD-fatigue. This work may be very useful in providing evidence to IBD nurses and doctors so that they routinely screen people with IBD for fatigue, and offer the right type of practical support.

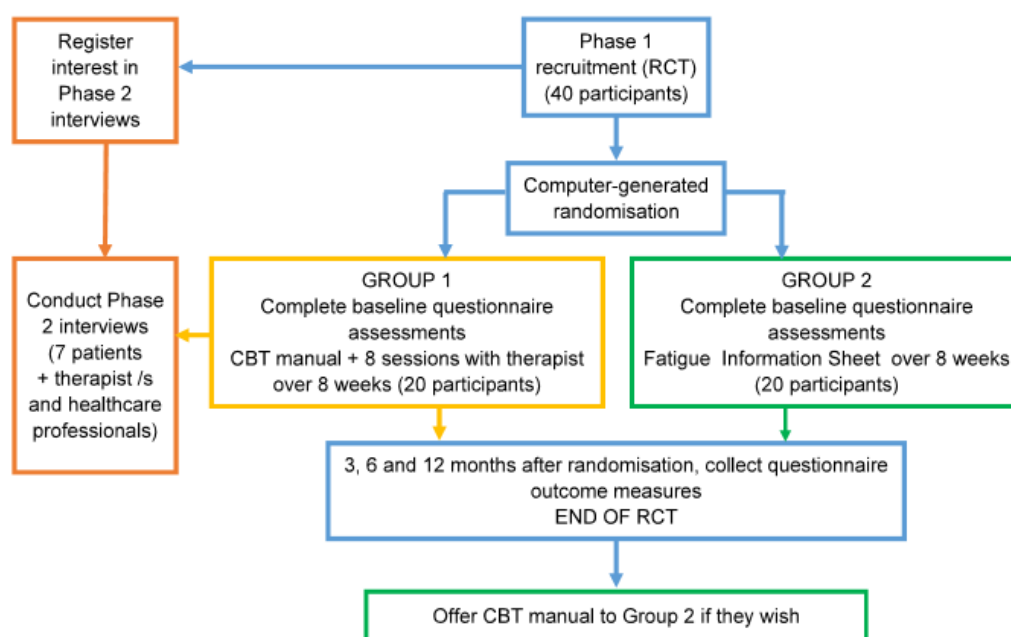
How will the research be done?

The project has two phases: a randomised controlled trial (RCT) and interviews. We are inviting you to take part in both. You can only take part in a Phase 2 interview if you have been involved in the Phase 1 RCT. Even if you show interest in the study, you may not be selected if more people offer to take part than we need (see Flow Chart, page 2).

Phase 1 is a randomised controlled trial (RCT). If you agree to take part, you will be **randomly allocated by chance** to EITHER Group 1 OR Group 2 of the study. If you are allocated to Group 1 you will be given a cognitive behavioural therapy (CBT) manual for the management of fatigue, and will have one 60-minute telephone/Skype session and seven 30-minute telephone/Skype sessions with a therapist over an eight week period. If you are allocated to Group 2, you will be given the Crohn's and Colitis UK "Fatigue and IBD" Information Sheet to use without any therapist help.

Phase 2 involves face to face/telephone/Skype interviews with one member of our research team. If you agree to take part in Phase 1 (RCT), you may also be invited to an interview after the RCT has finished. The researcher will ask you to talk about your experience of the RCT and the interventions, to get a detailed picture of the potential usefulness of the interventions. You do not have to decide about Phase 2 now. If you decide to take part in the Phase 1 RCT, we will ask you later if you are interested in also being interviewed. Even if you are interested in being interviewed, you may not be selected if more people offer to take part than we need.

It is important that you understand that you cannot select which group you are allocated to. If, following completion of the study, you have been allocated to Group 2 (Fatigue Information Sheet) you can request the self-management CBT manual received by Group 1 (without the therapist sessions) when the study has finished.



FLOW CHART FOR PHASES 1 and 2 (RCT and interviews)

Will you need to look at my medical records?

If you agree to take part we will collect some results from your records of routine blood tests that you have had. We will not ask for any additional blood tests, but we do need your permission to access your medical notes so we can record these.

Who can take part?

You can take part if you are aged 18 or over, your diagnosis of IBD has been confirmed with colonoscopy (endoscopy), you have no current flare-up of disease (not experiencing bowel symptoms usually associated with active flare), you are currently experiencing fatigue and you have a good command of written and spoken English. We are sorry, but you cannot take part if you do not meet these criteria, if you have had a cognitive behavioural intervention in the past year, or if you are currently taking part in a trial of a new drug.

What will happen if I agree to take part in the Phase 1 RCT?

If, after receiving this Information Sheet at your usual IBD clinic, you think that you could be interested in the study, we will ask you to provide us with your contact details. You will then have time to consider your participation in the study and discuss your decision with family, friends and the care team. In the next 2-5 days you will be contacted by a member of the research team to ask any questions, check that you understand what is involved, and that you cannot select which group you are allocated to. If you agree to take part in the study, you will be posted consent forms and baseline study questionnaires together with a return paid envelope. You will then be randomly allocated to either Group 1 or Group 2 of the study.

You will be asked to complete the study questionnaires on four occasions: at the start of the intervention (baseline), three months after randomisation (outcome 1), six months after randomisation (outcome 2), and twelve months after randomisation (outcome 3). These documents include several questionnaires which enable us to assess your disease activity, fatigue, quality of life, beliefs about fatigue and mood, and will help us show whether and how fatigue symptoms change during the course of the study. The questionnaires take about 10-15 minutes to complete. Your data will be archived safely and held for 10 years in accordance with sponsor requirements.

If you are randomly allocated to Group 1, you will be receive a cognitive behavioural therapy (CBT) manual for the management of fatigue. CBT is an evidence based psychological treatment. It is a way of helping people solve problems and improve the way we think and feel by learning new methods of coping and problem solving.

It is based on 2 principles:

- Our thoughts and beliefs are connected to our behaviours, moods and physical experiences and to the events in our lives.
- The perception of an event affects our emotional, behavioural and physiological responses to that event.

An initial 60-minute telephone/Skype appointment will be made with the therapist about 7 days after the receipt of the manual. You will then have seven, 30 minute sessions with the therapist, taking place weekly over an eight week period. You will have access to all your usual care. We will give you a choice of a time of day to complete the therapist-support sessions to suit your availability.

If you are randomly allocated to Group 2, you will receive the Crohn's and Colitis UK "Fatigue and IBD" Information Sheet . You will have access to all your usual care, but you will not receive the self-management CBT manual or the sessions with the therapist. This enables us to show whether the self-management CBT manual, or the Crohn's and Colitis UK "Fatigue and IBD" Information Sheet alone, is effective in managing fatigue. The interventions are not invasive, painful, nor do they require you to take additional medications. When this phase is over, you will not have to do anything for the study unless you have offered to take part in, and have been selected for, an interview.

What will happen if I agree to take part in, and am selected for a Phase 2 interview?

One of the researchers (Micol Artom) will contact you via telephone or Skype, according to your preference, to interview you at a time and draw which suits you. Micol will draw on your experience in taking part in the study to guide your interview, including what you found helpful or difficult, what you would change, whether you feel your fatigue symptoms have or have not improved, and how you feel about the results.

Micol has completed other IBD studies. She will be empathetic and understanding, and will encourage you to talk about your experiences in whichever way you feel most comfortable to do so. Before the interview begins, Micol will ask for your written consent, ensuring that you understand what you are being asked to do and that you agree to take part. The interview will be recorded on a digital audio device and typed up later.

What are the possible benefits?

We cannot guarantee that the interventions (self-management CBT manual + therapist support, or Crohn's and Colitis UK "Fatigue and IBD" Information Sheet) will improve your fatigue. If the interventions work, we will work with IBD nurses and researchers from King's College London to develop further interventions for the management of fatigue in people with IBD. If the intervention is not feasible or does not work, we will know that we need to do more research to develop other ways of helping people with IBD-fatigue. If you have requested it, we will send you a summary report of the findings when the study is completed.

What are the possible disadvantages or risks of taking part?

There may be a small risk of you becoming a little distressed when you complete the study questionnaires, when you are talking to the therapist about your fatigue, when reading the Fatigue Information Sheet, or when you are being interviewed, because thinking about your IBD or fatigue could be upsetting.

The study team is very experienced in the field of IBD and familiar with many of the issues you may be concerned about. All team members are experienced in offering reassurance to, and caring for, people in clinical settings and during research projects, and will support you at all stages of the study. You can get further support from the Crohn's & Colitis UK Helpline (Supportive Listening Service), which is available Mon-Fri, 1pm – 3.30pm, and 6.30pm – 9pm, except Bank Holidays in England. ☎ 0845 1303344 or 0121 7379931

What about confidentiality and anonymity?

Your personal details (name, age, diagnosis, hospital number) will be stored electronically in a secure, password protected Identification Log, and will remain confidential at all times. These details will only be used to contact you about this study and to track your progress through the study if you agree to take part.

Your personal data will be stored in line with the Data Protection Act and will not leave your hospital. An entry will be made in your hospital notes, informing your Consultant that you are taking part in this study. If you give us permission, we will also inform your GP.

If you are allocated to Group 1 in the RCT (CBT manual + therapist support) your identity will be known to the member of the research team who collects your consent and baseline data, and to the therapist who delivers your sessions.

If you are allocated to Group 2 in the RCT (Crohn's and Colitis UK "Fatigue and IBD" Information Sheet only) your identity will be known to the member of the research team who collects your consent and baseline data.

The study documents you complete will bear a Study ID number, and will not ask you for any information which could identify you. Your Study ID and your study data (the responses you give in the study documents you will complete at the start and end of your participation in the study) will be entered into a secure, password protected RCT electronic database. Your name and hospital number will not be on this RCT database. Your study data on the RCT database, will not contain information which could identify you.

If you agree to and are selected for an interview, your identity will also be known to the interviewer (Micol Artom) and to the Chief Investigator (Professor Norton). Professor Norton will keep a copy of the interview schedule (dates and locations) safely, and destroy it as soon as the schedule has been completed. Your personal details will not be known to any other member of the research team. The digital audio file of your interview will be sent via a secure file transfer service to a professional transcriber who types up the audio file. The transcriber, who has worked with us before, adheres to a professional code of conduct which respects confidentiality. Her copies of the audio file and the final transcription will be deleted once the transcription has been returned to us. Transcriptions and audio files will be kept securely on the central server at King's College, London, and only Micol Artom and Christine Norton will have access.

Before sharing your interview transcript with other research members, Micol will remove anything which might identify you, such as names, where you live, the hospital you attend or the nurse or doctor that you see in clinic. We will use your Study ID number or a pretend name in the transcript instead.

What will you do with the results of the study?

It is intended to publish the results of the research study in an appropriate medical journal. No patient will be individually identified in any report or publication. The results will be used to help us further develop and implement interventions for the management of fatigue in IBD.

Do I have to take part?

It is up to you to decide whether to take part or not. Even if you decide to take part, you are still free to withdraw from the Phase 1 RCT and from the Phase 2 interview at any time. You do not have to give a reason for withdrawing. If you withdraw from the study or lose mental capacity to participate further, we will keep and use any data we have already collected from you unless you state otherwise.

If you decide not to take part, this will in no way affect the care you receive from the IBD team at the hospital.

What happens now?

You will have at least 48 hours to decide if you want to take part or not. Then a member of the research team will contact you so you can ask any questions and enrol you to the study. You do not have to take part, the choice is yours. Please be aware that we may get many more offers to take part than we need so that even if you do want to take part, we may not be able to include you. We will let you know one way or the other.

Who has organised and reviewed this research?

The present study forms part of a PhD project at King's College London looking at fatigue in patients with IBD. The study has been reviewed by xxx Ethics Committee and has granted ethical approval on xx/xx/xxxx.

What if there is a problem?

If you have any complaint about the way you have been dealt with during the study or concerns about the study please contact the research team which will do their best to answer your questions. Please contact: Professor Christine Norton by email: christine.norton@kcl.ac.uk or telephone: +44 (0) 20 7848 3681.

If you have a complaint, you should talk to a member of the research team who will do their best to answer your questions. If you remain unhappy, you may be able to make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188. Address: PALS, KIC, Ground floor, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH.

This study is sponsored by King's College London University and Guy's & St Thomas' Foundation NHS Trust. The sponsor will at all times maintain adequate insurance in relation to the study independently.

CONTACT DETAILS

Any questions about the study should be directed to either to the PhD Researcher on the team or the Chief Investigator:

PhD Researcher

Micol Artom
Rm 1.32 24 James Clerk Maxwell Building
57 Waterloo Road
London SE1 8WA
Tel: + 079 30237160
Email: micol.artom@kcl.ac.uk

Chief investigator

Professor Christine Norton
Professor of Nursing
Rm 2.24 James Clerk Maxwell Building
57 Waterloo Road
London SE1 8WA
Tel: +44 (0) 20 7848 3681
Email: christine.norton@kcl.ac.uk

Please keep this information sheet for your own records.

Appendix XIII: Pilot RCT Patient Consent Form

Guy's and St Thomas'
NHS Foundation Trust 

STUDY ID:

Date:

**KING'S**
College
LONDON

PATIENT CONSENT FORM (RCT)

Study Title: MODIFY Fatigue

IRAS Number 212340

Version 1.1. Date: 12-09-2016

Chief Investigator: Professor Christine Norton, King's College London

Principal Investigator: Julie Duncan, IBD Clinical Nurse Specialist, Guy's & St Thomas' Hospitals

**Please
initial
box**

1. I confirm that I have read and understand the Patient information sheet dated **29-09-2016 (Version 1.3)** and that I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that I cannot choose whether I am allocated to Group 1 (CBT manual + therapist support) or Group 2 (Fatigue Information sheet only). ☐
3. I understand that I will be asked to complete a set of questionnaires once and will be asked to complete some of them again another three times (in 3, 6, 12 months' time) and I agree to do this. ☐
4. I understand that I may be asked to be interviewed about my experience in the study after its completion. ☐
5. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals from the research team at King's College London, who will collect information concerning my health. I give permission for these individuals to have access to my records when it is relevant to my taking part in the research study. ☐
6. I understand that my data will be anonymised before it is shared with any member of the research team, or used in publications or presentations. ☐
7. I understand that my identity will be known to the member of the team who screens me for this study, to the therapist if I am allocated to Group 1, and to the interviewer and Chief Investigator if I participate in Phase 2 interviews. ☐
8. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
9. I understand that even if I withdraw from the above study, or lose mental capacity to continue taking part and am withdrawn by the study team the data collected from me up until that time will be used in analysing the results, unless I specify not to do so. I understand that I will not be able to withdraw data from the study after the analysis of the data. ☐

CONTINUED ON BACK PAGE

STUDY ID:

Date:

CONTINUED FROM FRONT PAGE

10. I agree to any members of the research team using my anonymised data again in future studies, without the need to seek further permission from me.
11. I agree to my GP being informed of my participation in the study.
12. I agree to take part in the above study.

☐
☐
☐

Name of Patient

Date

Signature

Name of person taking consent

Date

Signature

Appendix XIV: Liverpool Central Committee ethical approval letter for pilot RCT

Page 1



North West - Liverpool Central Research Ethics Committee

3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 020 71048008

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

28 November 2016

Professor Christine Norton
Professor of Nursing
King's College London
Faculty of Nursing and Midwifery
King's College London
57 Waterloo Road, London
SE1 8WA

Dear Professor Norton

Study title:	Management of Inflammatory Bowel Disease-Fatigue: a Pilot Cognitive-Behavioural Therapy Intervention
REC reference:	16/NW/0791
Protocol number:	1.3
IRAS project ID:	212340

Thank you for responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Carol Ebenezer, nrescommittee.northwest-liverpoolcentral@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

The Committee pointed out that there is a typographical error in point 4 of the Consent Form (hare = share)

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at <http://www.rdforum.nhs.uk>

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/consultant information sheets or letters [General Practitioner Letter]	1.1	17 August 2016
Interview schedules or topic guides for participants [Patient Interview Schedule]	1.1	12 September 2016
Interview schedules or topic guides for participants [Therapist Interview Schedule]	1.1	12 September 2016
Interview schedules or topic guides for participants [HCP Interview Schedule]	1.1	12 September 2016
IRAS Application Form [IRAS_Form_07102016]		07 October 2016
Letters of invitation to participant [Patient Reminder Letter]	1.1	17 August 2016
Non-validated questionnaire [Demographic and clinical details form]	v.1.1	11 October 2016
Non-validated questionnaire [Follow-up questionnaire A]	v.1.1	11 October 2016
Non-validated questionnaire [Follow-up questionnaire B]	v.1.1	11 October 2016
Non-validated questionnaire [Demographic and clinical details form]	1.3	17 November 2016
Participant consent form [Staff Consent Form]	1.1	17 August 2016
Participant consent form [Patient Consent Form RCT]	1.3	17 November 2016
Participant consent form [Patient Consent Form Interviews]	1.2	17 November 2016
Participant information sheet (PIS) [Staff Information Sheet – Interviews]	1.2	29 September 2016
Participant information sheet (PIS) [Patient Information Sheet - RCT and Interviews]	1.4	17 November 2016
Research protocol or project proposal [Study Protocol]	1.3	29 September 2016
Summary CV for Chief Investigator (CI) [Professor Christine Norton CV]	1.1	07 October 2016

Summary CV for student [Micol Artom CV]		
Summary CV for supervisor (student research) [Professor Jackie Sturt CV]		
Summary CV for supervisor (student research) [Professor Rona Moss-Morris CV]		
Summary CV for supervisor (student research) [Dr Wladyslawa Czuber-Dochan CV]		
Validated questionnaire [Baseline Questionnaires]	1.2	25 August 2016
Validated questionnaire [Outcome Data 3- months follow-up 1]		
Validated questionnaire [Outcome data 3-months follow-up 2]		
Validated questionnaire [Outcome data 6-months follow-up]		
Validated questionnaire [Outcome data 12-months follow-up]		
Validated questionnaire [Inflammatory Bowel Disease Fatigue Scale]	v.1.1	11 October 2016
Validated questionnaire [United Kingdom Inflammatory Bowel Disease Quality of Life Questionnaire]	1.1.	11 October 2016
Validated questionnaire [Brief Illness Perceptions Questionnaire]	v.1.1.	11 October 2016
Validated questionnaire [Generalized Anxiety Disorder Questionnaire]	v.1.1	11 October 2016
Validated questionnaire [Patient Health Questionnaire]	v.1.1	11 October 2016
Validated questionnaire [Harvey Bradshaw Index]	v.1.1	11 October 2016
Validated questionnaire [Simple Clinical Colitis Index]	v.1.1	11 October 2016
Validated questionnaire [Epworth Sleepiness Scale]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training


We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

16/NW/0791

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely


pp.

Mrs Julie Brake
Chair

Email: nrescommittee.northwest-liverpoolcentral@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mr Keith Brennan, King's College London
Ms Jennifer Boston, Guy's & St Thomas' Foundation NHS Trust

Appendix XV: Structured feedback form for Patient and Public Involvement activity

PATIENT PUBLIC INVOLVEMENT TASK



Study Title: MODIFY Fatigue

Chief Investigator: Professor Christine Norton, King's College London

Co-investigators: Ms. Micol Artom, Professor Rona Moss-Morris, Professor Jackie Sturt, Dr. Wladyslawa Czuber-Dochan

ABOUT THE STUDY

Fatigue is one of the most common symptoms in patients with IBD and it can impact on patients' quality of life. This study aims to test interventions for the management of fatigue in patients with Inflammatory Bowel Disease (IBD) in a randomised controlled trial (RCT).

INSTRUCTIONS

Thank you for agreeing to take part in this Patient Public Involvement Task. Your involvement will be very valuable to make sure our research is designed in the right way. Attached to these instructions you will find a Patient Information Sheet, a Consent Form and a booklet with 8 questionnaires:

- 1) Please take the time to read the questionnaires and complete them carefully.
- 2) During the questionnaire completion please fill out the questions in the attached Feedback Form.
- 3) Please return the whole questionnaire pack to us either via postal mail utilizing the enclosed prepaid return envelope or as soon as possible.

If you have any additional questions about the research, please do not hesitate to contact us.

CONTACT DETAILS

Ms Micol Artom
PhD Research Fellow in Health Studies Research
King's College London
James Clerk Maxwell Building
57 Waterloo Road, London SE1 8WA
Mob: 07539946872
Email: micol.artom@kcl.ac.uk

FEEDBACK FORM



1. Was the **Patient Information Sheet** clear?

2. Is there anything you would add to/remove from the **Patient Information Sheet**?

3. Was the **Consent Form** clear and easy to complete?

4. How long did it take you to complete each individual questionnaire? How long did it take you to complete the whole questionnaire pack? *Please complete the table below.*

Questionnaire Name	Time in minutes
Demographic and Clinical Details Form	
Harvey–Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCCAI)	
IBD-Fatigue (IBD-F)	
Brief Illness Perceptions Questionnaire (BIPQ)	
Epworth Sleepiness Scale (ESS)	
Inflammatory Bowel Disease Questionnaire (IBDQ)	
Generalized Anxiety and Disorder Scale (GAD-7)	
Patient Health Questionnaire (PHQ-9)	
Total time for the 8 questionnaires	

FEEDBACK FORM



5. Did you complete the questionnaire pack all in one go? *If more than one session, please describe.*

6. Which **two** questionnaires did you enjoy completing the most?

7. Which **two** questionnaires did you enjoy completing the least? *Please explain why.*

8. If these were the questionnaires you had to fill out, would you agree to take part in the study?

9. Do you have any additional comments about your experience of filling out the questionnaires, the Information Sheet and Consent Form or the study in general?

THANK YOU FOR YOUR FEEDBACK

Appendix XVI: Crohn's and Colitis UK Fatigue Information Sheet



FIGHTING
INFLAMMATORY
BOWEL DISEASE
TOGETHER



INFORMATION SHEET

FATIGUE AND IBD

INTRODUCTION

Many people with Ulcerative Colitis and Crohn's Disease experience fatigue, which affects each person differently. This information sheet describes the fatigue that may occur with Inflammatory Bowel Disease, explains what may cause it, and suggests possible ways to reduce it. Much of the information is based on results from the four-year Crohn's and Colitis UK Fatigue in IBD study.

“

Just feeling very, very weary, and no inner energy...I'm "bone weary" is the old way of describing it.

”

Fatigue in IBD study participant

WHAT IS FATIGUE?

Fatigue can be described as an overwhelming sense of continuing tiredness, lack of energy, or feeling of exhaustion that is not relieved after rest or sleep. It is far more than the ordinary and usual tiredness that anyone may feel after they have done a lot of physical or mental activity. For people with IBD, fatigue can feel physical (a lack of energy or strength), mental (a lack of motivation, concentration or alertness) or a combination of the two.

Fatigue can be very unpredictable, varying from day to day or even hour to hour. It can come on suddenly with no warning. People sometimes describe it as like 'hitting a brick wall'.

HOW COMMON IS FATIGUE IN IBD?

Fatigue in IBD is very common – over three-quarters of people experience fatigue during an IBD flare-up.

There doesn't seem to be a major difference in the levels of fatigue between people with Ulcerative Colitis and people with Crohn's. However, some research suggests that fatigue may be more common in women, and may be worse in people with Crohn's.

Many people find that their fatigue improves as their IBD improves. For some, there can be a time lag of weeks or months before they regain their normal energy levels. Sometimes the fatigue doesn't go away even when other IBD symptoms are under control. Fatigue continues to affect two in every five people whose IBD is in remission.

WHAT CAUSES FATIGUE IN IBD?

There are many factors that have been associated with fatigue in IBD. It is likely that these factors influence each other, so you may find that a combination could be contributing to your fatigue.

Inflammation

During a flare-up, fatigue may be caused by the body's response to inflammation and illness. Chemical signals that are produced during inflammation act directly on the brain to cause sickness behaviours – such as lack of motivation, tiredness and loss of appetite.

Pain

Pain is a common symptom for people with IBD and may be caused by a number of factors, including inflammation, blockages and bloating in the gut, along with pain caused by manifestations of IBD in other parts of the body, such as arthritis. In some cases, pain will remain during periods of remission. Dealing with pain can be draining. Pain may contribute to fatigue through poor sleep quality, reduced physical activity and emotional and psychological distress.

Nutritional deficiencies

Nutrient and vitamin deficiencies in people with IBD may be caused by diarrhoea, a loss of appetite or poor absorption through the inflamed gut wall.

Anaemia, a common complication of IBD, may worsen fatigue. People with anaemia carry less oxygen in their blood, which can mean they easily become exhausted.

In people with IBD, anaemia can occur due to:

- a persistently low level of haemoglobin, a protein in red blood cells that carries oxygen around the body. This can result from poor absorption of iron in the gut
- low numbers of red blood cells, which may be caused by loss of blood from the inflamed wall of the gut, or by deficiencies in vitamins B12 and/or folate

Low vitamin D levels may also contribute to fatigue. Vitamin D is important for keeping your bones, muscles and immune system healthy.

Emotional stress/psychological disorders

Anxiety, depression and stress are consistently associated with fatigue in people with IBD – however it is not clear whether anxiety, depression or stress cause fatigue, or are a result of fatigue. Emotional and psychological stress can trigger inflammation and pain, and as described above, these factors may contribute to fatigue.

Medication

Steroids and drugs that alter the immune system – including azathioprine, mercaptopurine and methotrexate – have been linked to fatigue in some people.

Disturbed sleep

Poor sleep quality may be the result of pain or having to use the toilet multiple times during the night.

Other possible causes

It is unclear why fatigue doesn't always get better when the IBD does, and why it can continue even during remission.

In some cases, people may think they are in remission because they do not have any obvious symptoms of IBD, such as diarrhoea or bleeding. But they may still have some inflammation in the wall of the gut that could be causing their fatigue.

“I'll be functioning in what I consider to be a perfectly normal way and feeling great one minute. And the next minute, for no reason whatsoever, I'll suddenly drain and have no energy.”

Fatigue in IBD study participant

FATIGUE AND IBD

“

Go to work, barely get through the day and then coming home and then just crashing out, and I couldn't do anything because I didn't have the energy.

”

Fatigue in IBD study participant

In the Crohn's and Colitis UK Fatigue in IBD study, available at www.fatigueinIBD.co.uk, a number of other factors were suggested as possible causes for fatigue. These included:

- Diet and alcohol
- Being overweight or underweight
- Other health problems
- Extremes of weather
- Lack of support or understanding

Any of these factors may lead to fatigue. However, in some people there is no obvious explanation.

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis or ME, is a long-term illness with many symptoms, the most common of which are extreme tiredness and generally feeling unwell. CFS may be diagnosed if you suffer from long-term fatigue that can't be explained by other causes. There is increasing evidence that inflammation in the gut may contribute to the development of CFS.

HOW DOES FATIGUE AFFECT PEOPLE WITH IBD?

Fatigue can affect many aspects of life. Some people find it difficult to perform everyday functions when their IBD is active, because of both bowel symptoms and fatigue. Fatigue may affect the lives of people with IBD in many different ways:

- **Physical Activity**
Low energy levels can make it very hard to take part in physical activities, such as sport. Some people find they don't have the energy to carry out everyday tasks such as driving, housework or collecting the children from school. On very bad days, even walking from one room to another may require great effort.
- **Memory and concentration**
Some people find that fatigue makes it difficult to think logically. You may find that it can affect your concentration and memory. When you are very fatigued, you may feel you cannot speak properly, and may stumble over your words. Some people call this 'brain fog'. See **Talking about fatigue** below.
- **Social Activities**
Unpredictable fatigue can make it difficult to take part in social activities. This may mean that you refrain from going on holiday, travelling, socialising, or taking part in hobbies or interests.
- **Emotions**
Fatigue can have an effect on your emotions. If you can't do as much as you would like, you may feel frustrated and angry. Some people feel isolated and lonely if they find it difficult to socialise with friends. This can lead to low confidence and depression. You may find it helpful to discuss your feelings with a counsellor. To find out more, see our information sheet **Counselling for IBD**.
- **Relationships**
Some people find that fatigue has a negative effect on their relationships with partners, friends and family. For example, some people may feel that,

“

I've sat in the kitchen and cried, because I can't make a decision on something and the children are asking. And I'm so tired.

”

Fatigue in IBD study participant

3

Crohn's & Colitis UK | www.crohnsandcolitis.org.uk

“

Sometimes I don't realise I have been suffering from fatigue until my energy levels have returned to normal and I look back.

”

Jo, age 50, diagnosed with Ulcerative Colitis in 1999

“

I think there can be a bit of a stigma attached to fatigue where people might struggle through it not wanting to admit to it for fear of being seen as lazy.

”

Shirley, age 39, diagnosed with Ulcerative Colitis in 1993

“

I think my family are very supportive and so are my friends, because I've told them how I feel...It's up to us to tell them how we are feeling.

”

Fatigue in IBD study participant

because their condition cannot be seen, their family and friends don't appreciate how fatigued they are. You may find that you feel guilty if your partner or family have to do extra things to help, or if they miss out on doing things with you. Being open and honest about your condition may be helpful. If fatigue is having an impact on your sex life, you may find our information sheet **Sexual Relationships and IBD** helpful.

- **Work and education**

Fatigue can affect employment and education. Some people with fatigue may be able to manage a full-time job, while others may struggle with such a commitment. Some experience fatigue so strongly that they have to give up work. Working part-time or reducing the number of hours worked each day can sometimes help manage fatigue, but this might have financial implications. Our information sheet, **Employment and IBD: A guide for employees** provides more information on your options and how you might be protected by law.

Students with fatigue may find studying difficult, and may worry that fatigue will limit their achievements and job aspirations. Schools and universities can often work with students to help them cope with periods of IBD-related fatigue, such as setting extended deadlines or giving extra time during exams. See **Students with IBD: A guide for students** for more information.

TALKING ABOUT FATIGUE

It can be difficult to discuss fatigue and to explain the problems it causes. You might find it difficult to talk to your doctor about your fatigue, and therefore miss out on receiving help.

During the Crohn's and Colitis UK Fatigue in IBD study, people with IBD used some of the following words to describe their fatigue:

- Brain fog
- A big black hole
- Being woozy or fuzzy
- Zombie mode
- Overwhelming heaviness
- Just shattered
- Completely wiped out

You may find it helpful to use some of these descriptions when you are talking to your healthcare team.

Some doctors and nurses are not aware how much fatigue can affect people with IBD, so they may not ask about it during an appointment. Fatigue is not a personal failing, and is nothing to be embarrassed about. It's important that you discuss all of your symptoms and concerns with your doctor or IBD team. Of course, telling doctors and nurses you are tired doesn't ring the same alarm bells as saying you have an immediately dangerous symptom. But, living with persistent fatigue is unacceptable, so you may have to push more than usual to ensure you get the proper care you need.

“

There's a whole range of symptoms that employers, GPs, family, should be aware of as a result of your condition. 'Tiredness' is just one of them.”

—
Fatigue in IBD study participant

“

I try and take each day as it comes. I have learnt that I need to take it easy sometimes, but it hasn't stopped me doing the things I enjoy. I like running, so I get out for a run when I feel up to it.”

”

—
Andy, age 36, diagnosed with Ulcerative Colitis in 2007

MEASURING FATIGUE

The Crohn's and Colitis UK Fatigue in IBD study, funded by the Big Lottery Fund, led to the creation of a new IBD Fatigue Scale to measure the severity and impact of fatigue. You can find this at www.fatigueinIBD.co.uk/questionnaire. If you find it difficult to talk about fatigue, you may find it helpful to print the questionnaire and show it to your healthcare team.

There is also a checklist you can use to consider possible causes of your fatigue, in order to make sure nothing is overlooked. You will be able to fill in some items yourself, but for others you will need a doctor or nurse to give you the information. You can find the checklist at www.fatigueinIBD.co.uk/checklist.

WHAT CAN I DO TO REDUCE MY FATIGUE?

There are a range of actions you can take to reduce or manage your fatigue.

The first and most important thing to do is to ask your doctor or IBD nurse to check that you do not have active IBD. This might be done with a blood test or stool test. If your IBD is active, then you will need treatment to see whether your fatigue improves as your IBD improves. This may mean changing the dose or type of medicine that you are taking. You should also speak to your doctor if you think your medication may be causing your fatigue, as they might be able to adjust the dose or find an alternative medicine.

If your IBD is in remission, you could ask for a blood test to check for anaemia, iron stores, vitamin B12, and other chemical or nutrient deficiencies.

Those experiencing emotional or psychological stress should speak to their GP or IBD team about accessing specialist support to help cope with this. Research has shown that counselling or 'talking therapies', such as cognitive behavioural therapy, can reduce stress and depression, and improve quality of life in people with IBD – and may also be beneficial in improving fatigue. For more information on the different types of counselling and how it may help you, see our information sheet **Counselling and IBD**.

There is some evidence that low to moderate intensity physical activity may reduce IBD fatigue. You could try gradually to increase the amount of physical exercise you do, while being careful not to overdo it. This can be simple activities, such as walking rather than catching the bus for short journeys, or going to exercise classes. It is important to achieve the right balance between doing too much and exhausting yourself, and not doing enough to make a difference. You might need to build up your activity level slowly over several weeks. See our booklet **Living with IBD** for tips on exercising with IBD.

If you smoke, stopping smoking can also help to reduce IBD fatigue. You may find our information sheet **Smoking and IBD** helpful.

If pain is contributing to your fatigue, you may wish to discuss pain management strategies with your IBD care team. There are a number of options that may help with pain in IBD, many of which have already been mentioned above as ways to tackle fatigue. These include drug treatments, exercise or physical therapy, stopping smoking and counselling.

For more information on how to increase your physical activity, or for advice on stopping smoking, visit www.nhs.uk/livewell.

5

Crohn's & Colitis UK | www.crohnsandcolitis.org.uk

CAN CHANGING MY DIET REDUCE MY FATIGUE?

Diet may also play a part in causing IBD fatigue, especially if you aren't receiving the amounts of calories and nutrients that are right for you.

There are many foods that may help alleviate various deficiencies, including vitamin B12, iron, folate and vitamin D, which is also synthesised in the skin during exposure to sunlight. Your doctor, IBD team or dietician can offer advice. For information on nutritional supplements such as iron, folic acid (a synthetic form of folate), vitamin B12 and others, you may want to read our information sheet **Other Treatments for IBD**.

Some people have found that taking other supplements, such as omega-3 oils (found naturally in oily fish and some other foods) improves their fatigue. However, there is little scientific evidence to support this. Check with your IBD team before taking any supplements or making major changes in your diet.

Some people find that during a flare-up they cannot tolerate certain foods. During remission, you should try to eat as balanced and healthy a diet as possible. Foods containing carbohydrates are a major source of energy. There are two types of carbohydrate – simple and complex. Foods containing complex carbohydrates (such as cereals or porridge) can provide you with longer-term energy. Foods containing simple carbohydrates (such as sugary sweets, cakes and biscuits) provide quick bursts of energy, but this energy only lasts a short time.

Although there is currently little scientific evidence, some people find that following a gluten-free diet reduces their fatigue.

Eating smaller meals and healthy snacks more frequently, rather than larger meals less often, may help you keep your energy levels up throughout the day. You could try eating every three to four hours to see if this helps your fatigue.

For more information about how to manage a healthy diet, see our booklet **Food and IBD**.

IS THERE ANYTHING ELSE I CAN DO TO REDUCE MY FATIGUE?

There are a variety of other ways in which people with IBD help themselves manage fatigue, for example:

- Frequent breaks and rest
- Good-quality sleep
- Complementary and alternative therapies such as mindfulness, acupuncture, yoga or homeopathy
- Physiotherapy and exercise
- Flexible working hours
- Planning ahead
- Reducing stress

Two further points to remember are to prioritise the demands on you, and to pace yourself.

“
I would have a rest in the morning and a rest in the afternoon. And that was how I got through the day.”

Fatigue in IBD study participant

FATIGUE AND IBD

What works for some people may not work for others. Learning more about your body, and what may trigger your fatigue, can be helpful.

Talk to your doctor or nurse about your fatigue, and explore methods that might help you, rather than simply accepting it and missing out on support that is available. There are many methods – from resting to exercising – that you can try yourself to discover what works for you. If you need further help, your healthcare team may also be able to refer you to other services such as counselling or specialist chronic fatigue services.

FURTHER HELP

Fatigue Microsite
www.fatigueinIBD.co.uk

NHS Live Well
www.nhs.uk/livewell

HOW WE CAN HELP YOU

We offer more than 45 publications on many aspects of Crohn's Disease, Ulcerative Colitis and other forms of Inflammatory Bowel Disease. You may be interested in our comprehensive booklets on each disease, as well as the following publications:

- Living with IBD
- Counselling for IBD
- Food and IBD

All publications are available to download from www.crohnsandcolitis.org.uk.
The complete list is here: www.crohnsandcolitis.org.uk/about-inflammatorybowel-disease/quick-list.

Health professionals can order some publications in bulk by using our online ordering system, available from the webpage above.

If you would like a printed copy of a booklet or information sheet, please contact our helpline.

Our helpline is a confidential service providing information and support to anyone affected by Inflammatory Bowel Disease.

Our team can:

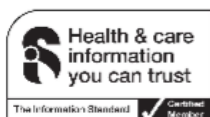
- help you understand more about IBD, diagnosis and treatment options
- provide information to help you to live well with your condition
- help you understand and access disability benefits
- be there to listen if you need someone to talk to
- put you in touch with a trained support volunteer who has a personal experience of IBD

Call us on **0300 222 5700** or email info@crohnsandcolitis.org.uk

See our website for LiveChat: www.crohnsandcolitis.org.uk/livechat

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Fatigue and IBD - Edition 2
Last Review - December 2017
Next planned review - 2020

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We hope that you have found this leaflet helpful and relevant. If you would like more information about the sources of evidence on which it is based, or details of any conflicts of interest, or if you have any comments or suggestions for improvements, please email the Publications Team at publications@crohnsandcolitis.org.uk. You can also write to us at Crohn's and Colitis UK, 45 Grosvenor Road, St Albans, AL1 3AW or contact us through the **Information Line: 0300 222 5700**.

ABOUT CROHN'S & COLITIS UK

We are a **national** charity established in 1979. Our aim is to improve life for anyone affected by Inflammatory Bowel Diseases. We have over 35,000 members and 50 Local Networks throughout the UK. Membership costs start from £15 per year with concessionary rates for anyone experiencing financial hardship or on a low income.

This publication is available free of charge, but we would not be able to do this without our supporters and members. Please consider making a donation or becoming a member of Crohn's and Colitis UK. To find out how, call **01727 734465** or visit www.crohnsandcolitis.org.uk

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Appendix XVII: Pilot RCT study questionnaire booklet



MODIFY Fatigue

Management of Inflammatory Bowel Disease-Fatigue: a Pilot Cognitive-Behavioural Therapy Intervention Study

IRAS Number 212340

STUDY ID:

Data Code: A

Data Name: Baseline data

Date you completed this form:/...../..... e.g. 12/ 02 / 2016
dd mm yyyy

This form collects information from you which will tell us how you are in terms of your IBD, your fatigue, your quality of life and your mood and thoughts. The form includes several individual questionnaires, each with its own instructions or guidance notes. Please read carefully, and answer the questions as honestly as possible. You may find that some questionnaires ask similar questions— please respond to all questions, even if you feel you have already answered. We will compare your answers with those you will give us after the end of the study to show what effect, if any, participating in the study has had.

Demographic and Clinical Details Form

Please tick one answer only

1. Gender Male ☐
 Female ☐

2. Age (Years) _____

3. When did your inflammatory bowel disease (IBD) symptoms start?

Month (MM, e.g. 02) _____

Year (yyyy, e.g. 1990) _____

4. What is the highest level of education you have completed? *Please tick one answer only*

- School up to age 16 years ☐
 School or College 16 to 18 years ☐
 Higher Education after 18 years ☐

5. Do you do aerobic exercise (physical activity that makes you sweat, causes you to breathe harder, and gets your heart beating faster than at rest)? *Please tick one answer only*

- More than 30 minutes of aerobic exercise per week ☐
 Less than 30 minutes of aerobic exercise per week ☐

6. Do you smoke? *Please tick one answer only*

- Yes ☐
 Ex-smoker ☐
 No ☐

7. Are you currently? *Please tick one answer only, if other please specify*

- Married/Living with partner ☐
 Widowed ☐
 Divorced/Separated ☐
 Other (_____)

8. During the past month were you? *Please tick one answer only*

- | | |
|----------------------------|--------------------------|
| Working/Studying Full time | <input type="checkbox"/> |
| Working/Studying Part time | <input type="checkbox"/> |
| Retired | <input type="checkbox"/> |
| Full time house keeping | <input type="checkbox"/> |
| Not working | <input type="checkbox"/> |

9. What members of family live with you? *Please tick one answer only*

- | | |
|---------------------------------------|--------------------------|
| Live alone | <input type="checkbox"/> |
| Live with spouse/partner | <input type="checkbox"/> |
| Live with spouse/partner and children | <input type="checkbox"/> |
| Single parent with children | <input type="checkbox"/> |
| Live with other relatives | <input type="checkbox"/> |
| Live with friends | <input type="checkbox"/> |

10. Would you like to be informed about the results of the study? *Please tick one answer only*

- | | |
|-----|--------------------------|
| Yes | <input type="checkbox"/> |
| No | <input type="checkbox"/> |

Please complete ONE disease activity index (page 4 OR page 5) which is relevant to you.

Simple Index of Crohn's Disease Activity (Harvey & Bradshaw 1980)

Complete this section if you have Crohn's disease or Crohn's colitis.

Record how you have been over the past 24 hours. If you have UC go to next page.

A. General Wellbeing *Please select one ...*

- ☐ Very well
- ☐ Slightly below par
- ☐ Poor
- ☐ Very poor
- ☐ Terrible

B. Abdominal Pain *Please select one ...*

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

C. Number of liquid stools in the last 24 hours *Please write answer in digits in box below...*

D. Abdominal mass (abdomen feels lumpy/swollen) *Please select one ...*

- ☐ None
- ☐ Dubious
- ☐ Definite
- ☐ Definite and tender

E. Complications (issues related to Crohn's disease which affect other parts of the body)

Please tick all that apply at the moment

- ☐ Painful joints/arthritis
- ☐ Anal fissure/fistula/abscess
- ☐ Mouth ulcers
- ☐ Skin nodules or ulcers (including pyoderma and erythema nodosum)
- ☐ Eye pain or inflammation (red eyes)
- ☐ Liver problems (eg primary sclerosing cholangitis)
- ☐ None of these apply at the moment

Simple Clinical Colitis Activity Index (Walmsley et al 1998)

Complete this section if you have Ulcerative colitis, proctitis, or IBD unclassified.
Record how you have been over the past 24 hours. Ignore this page if you have CD.

A. Bowel frequency (day) Please indicate the number of bowel movements during the day

- ☐ 0
- ☐ 1-3
- ☐ 4-6
- ☐ 7-9
- ☐ more than 9

B. Bowel frequency (night) Please indicate the number of bowel movements at night

- ☐ 0
- ☐ 1-3
- ☐ 4-6

C. Urgency of defecation (having bowels open) Please select one ...

- ☐ No urgency/hurry today
- ☐ Hurry
- ☐ Immediately
- ☐ Incontinence

D. Blood in stool Please select one ...

- ☐ No blood in stool today
- ☐ Trace
- ☐ Occasionally frank (frank = obvious/visible)
- ☐ Usually frank

E. General Wellbeing Please select one ...

- ☐ Very well
- ☐ Slightly below par
- ☐ Poor
- ☐ Very poor
- ☐ Terrible

E. Complications (issues related to Ulcerative colitis which affect other parts of the body)

Please tick all that apply at the moment

- ☐ Painful joints/arthritis
- ☐ Anal fissure/fistula/abscess
- ☐ Mouth ulcers
- ☐ Skin nodules or ulcers (including pyoderma and erythema nodosum)
- ☐ Eye pain or inflammation (red eyes)
- ☐ Liver problems (e.g. primary sclerosing cholangitis)
- ☐ None of these apply at the moment

Baseline data v1.3 17-11-2016

Inflammatory Bowel Disease-Fatigue (IBD-F)

Please tick <u>ONE</u> number for each question	Score from 0 - 4 with				
	0 = no fatigue		severe fatigue = 4		
What is your fatigue level right NOW	0	1	2	3	4
2. What was your HIGHEST fatigue level in the past two	0	1	2	3	4
3. What was your LOWEST fatigue level in the past two	0	1	2	3	4
4. What was your AVERAGE fatigue level in the past two	0	1	2	3	4
5. How much of your waking time have you felt fatigued in the past two weeks	0 None of the time	1 Some of the time	2 Often	3 Most of the time	4 All the time

SECTION I - Fatigue Assessment Scale

This section of the questionnaire will identify fatigue, its severity, frequency and duration.

Sometimes people with inflammatory bowel disease feel fatigued. The term 'fatigue' is used throughout the questionnaire. Fatigue has been defined as a sense of continuing tiredness, with periods of sudden and overwhelming lack of energy or feeling of exhaustion that is not relieved following rest or sleep.

SECTION II – IBD-Fatigue Impact on Daily Activities Scale

This section assesses the perceived impact of fatigue on your daily activities in the **past two weeks**.

Please answer all the questions. The possible answers to the questions are: None of the time - 0; Some of the time - 1; Often - 2; Most of the time - 3; All of the time - 4.

If a particular activity does not apply to you, for example you do not drive, please select N/A.

Please tick only ONE answer for each question reflecting on the past two weeks						
	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
1. I had to nap during the day because of fatigue	0	1	2	3	4	
2. Fatigue stopped me from going out to social events	0	1	2	3	4	
3. I was not able to go to work or college because of fatigue	0	1	2	3	4	N/A
4. My performance at work or education was affected by fatigue	0	1	2	3	4	N/A
5. I had problems concentrating because of fatigue	0	1	2	3	4	
6. I had difficulty motivating myself because of fatigue	0	1	2	3	4	
7. I could not wash and dress myself because of fatigue	0	1	2	3	4	
8. I had difficulty with walking because of fatigue	0	1	2	3	4	
9. I was unable to drive as much as I need to because of fatigue	0	1	2	3	4	N/A
10. I was not able to do as much physical exercise as I wanted to because of fatigue	0	1	2	3	4	

Baseline data v1.3 17-11-2016

I was not able to do as much physical exercise as I wanted to because of fatigue	0	1	2	3	4	
Please tick only ONE answer for each question reflecting on the past two weeks	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
11. I had difficulty continuing with my hobbies/interests because of fatigue	0	1	2	3	4	
12. My emotional relationship with my partner was affected by fatigue	0	1	2	3	4	N/A
13. My sexual relationship with my partner was affected by fatigue	0	1	2	3	4	N/A
14. My relationship with my children was affected by fatigue	0	1	2	3	4	N/A
15. I was low in mood because of fatigue	0	1	2	3	4	
16. I felt isolated because of fatigue	0	1	2	3	4	
17. My memory was affected because of fatigue	0	1	2	3	4	
18. I made mistakes because of fatigue	0	1	2	3	4	
19. Fatigue made me irritable	0	1	2	3	4	
20. Fatigue made me frustrated	0	1	2	3	4	
21. I got words mixed up because of fatigue	0	1	2	3	4	
22. Fatigue stopped me from enjoying life	0	1	2	3	4	
23. Fatigue stopped me from having a fulfilling life	0	1	2	3	4	
24. My self-esteem was affected by fatigue	0	1	2	3	4	
25. Fatigue affected my confidence	0	1	2	3	4	

Please tick only ONE answer for each question reflecting on the past two weeks						
	None of the time	Some of the time	Often	Most of the time	All of the time	Not applicable
26. Fatigue made me feel unhappy	0	1	2	3	4	
27. I had difficulties sleeping at night because of fatigue	0	1	2	3	4	
28. Fatigue affected my ability to do all my normal household activities	0	1	2	3	4	
29. I had to ask others for help because of fatigue	0	1	2	3	4	
30. Quality of my life was affected by fatigue	0	1	2	3	4	

Baseline data v1.3 17-11-2016

Belief Illness Perception Questionnaire (B-IPQ)

For the following questions, please *circle* a number that best corresponds to your views:

a. How much do fatigue symptoms affect you currently?

No affect at all 0 1 2 3 4 5 6 7 8 9 10 Severely affects me currently

b. How long do you think your fatigue symptoms will continue?

A very short time 0 1 2 3 4 5 6 7 8 9 10 Forever

c. How much control do you feel you have over your fatigue?

Absolutely no control 0 1 2 3 4 5 6 7 8 9 10 Extreme amount of control

d. How much do you think your treatment can help your fatigue symptoms?

Not at all 0 1 2 3 4 5 6 7 8 9 10 Extremely helpful

e. How concerned are you about your fatigue symptoms?

Not at all concerned 0 1 2 3 4 5 6 7 8 9 10 Extremely concerned

f. How well do you feel you understand your fatigue symptoms?

Don't understand at all 0 1 2 3 4 5 6 7 8 9 10 Understand very clearly

g. How much does your fatigue symptoms affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

Not at all affected emotionally 0 1 2 3 4 5 6 7 8 9 10 Extremely affected emotionally

Epworth Sleepiness Scale (ESS)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate *number* for each situation:

0 = No chance of dozing
1 = Slight chance of dozing

2 = Moderate chance of dozing
3 = High chance of dozing

SITUATION

CHANCE OF DOZING

Sitting and reading

Watching TV

Sitting inactive in a public place (e.g. a theatre or a meeting)

As a passenger in a car for an hour without a break

Lying down to rest in the afternoon when the circumstances permit

Sitting and talking to someone

Sitting quietly after a lunch without alcohol

In a car, while stopped for a few minutes in traffic

TOTAL

Baseline data v1.3 17-11-2016

The UK Inflammatory Bowel Disease Questionnaire (IBDQ)

The following questions ask about your bowel problem and how it affected your life over the last two weeks. Please *tick* one answer for each of the questions. If you are unsure about how to answer any question, just give the best answer you can.

1. On how many days over the last two weeks have you had loose or runny bowel movements?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

2. On how many days over the last two weeks have you felt tired?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

3. In the last two weeks have you felt frustrated?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

4. In the last two weeks, has your bowel condition prevented you from carrying out your work or other normal activities?

- ☐ No, not at all
- ☐ Yes, for one or two days
- ☐ Yes, for three to seven days
- ☐ Yes, for eight to fourteen days (i.e. more than every other day)

5. On how many days over the last two weeks have you opened your bowels more than three times a day?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

6. On how many days over the last two weeks have you felt full of energy?

- ☐ None
- ☐ On one to two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (ie more than every other day)

7. In the last two weeks have you been worried about being admitted to hospital because of your bowel problem?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

8. In the last two weeks did your bowel condition prevent you from going out socially?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all the time
- ☐ Does not apply to me

9. On how many days over the last two weeks have your bowels opened accidentally?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (ie more than every other day)

10. On how many days over the last two weeks have you felt generally unwell?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

11. In the last two weeks have you felt the need to keep close to a toilet?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

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12. In the last two weeks, has your bowel condition affected your leisure or sports activities?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time
- ☐ Does not apply to me

13. On how many days over the last two weeks have you felt pain in your abdomen?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

14. On how many nights over the last two weeks have you been unable to sleep well (days if you are a shift worker)?

- ☐ None
- ☐ On one or two nights only
- ☐ On three to seven nights
- ☐ On eight to fourteen nights (i.e. more than every other night)

15. In the last two weeks have you felt depressed?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

16. In the last two weeks have you had to avoid attending events where there was no toilet close at hand?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

17. On how many days over the last 2 weeks, have you had a problem with large amounts of wind?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

18. On how many days over the last two weeks have you felt off your food?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (ie more than every other day)

19. Many patients with bowel problems have worries about their illness. How often during the last two weeks have you felt worried?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

20. On how many days over the last two weeks has your abdomen felt bloated?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

21. In the last two weeks have you felt relaxed?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

22. On how many days over the last two weeks have you noticed blood with your bowel movements?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (ie more than every other day)

23. In the last two weeks have you been embarrassed by your bowel problem?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

18. On how many days over the last two weeks have you felt off your food?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (ie more than every other day)

19. Many patients with bowel problems have worries about their illness. How often during the last two weeks have you felt worried?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

20. On how many days over the last two weeks has your abdomen felt bloated?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

21. In the last two weeks have you felt relaxed?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

22. On how many days over the last two weeks have you noticed blood with your bowel movements?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (ie more than every other day)

23. In the last two weeks have you been embarrassed by your bowel problem?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

24. On how many days over the last two weeks have you wanted to go back to the toilet immediately after you thought you had emptied your bowels?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

25. In the last two weeks have you felt upset?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

26. On how many days over the last two weeks have you had to rush to the toilet?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

27. In the last two weeks have you felt angry as a result of your bowel problem?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

28. In the last two weeks, has your sex life been affected by your bowel problem?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time
- ☐ Does not apply to me

29. On how many days over the last two weeks have you felt sick?

- ☐ None
- ☐ On one or two days only
- ☐ On three to seven days
- ☐ On eight to fourteen days (i.e. more than every other day)

30. In the last two weeks have you felt irritable?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

31. In the last two weeks have you felt lack of sympathy from others?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

32. In the last two weeks have you felt happy?

- ☐ No, not at all
- ☐ Yes, some of the time
- ☐ Yes, most of the time
- ☐ Yes, all of the time

Generalized Anxiety Disorder Scale (GAD-7)

Please circle the answer for each question which is most relevant to you

Over the last <u>two weeks</u> , how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

If you ticked any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission

Patient Health Questionnaire (PHQ-9)

Please circle the answer for each question which is most relevant to you

Over the <u>last two weeks</u> , how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things.....	0	1	2	3
2. Feeling down, depressed, or hopeless.....	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much.....	0	1	2	3
4. Feeling tired or having little energy.....	0	1	2	3
5. Poor appetite or overeating.....	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down.....	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.....	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual.....	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way.....	0	1	2	3

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission

Baseline data v1.3 17-11-2016

Please double check that you have
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Appendix XVIII: Papers reporting on the development of interventions utilising the MRC framework for the development and evaluation of complex interventions

Study (First Author, Date)	Country	Intervention	MRC version	MRC phase/step	Methods
Barley et al. (2012)	UK	Nurse-led intervention to improve mood and cardiac outcomes in depressed coronary health disease (CHD) patients	2008	1a. Identifying the evidenced base	<ul style="list-style-type: none"> – Systematic review of studies of depression management in the UK – Interviews with healthcare professionals to determine preferences for the future intervention – Interviews with patients with CHD and depression needs for the future intervention
				1b. Identifying/developing theory	<ul style="list-style-type: none"> – Multidisciplinary project group and independent steering group meetings to integrate findings – Iterative evidence review to support choices for the intervention content
				1c. Modelling the process and outcomes	<ul style="list-style-type: none"> – Focus groups to determine the potential acceptability of the intervention to patients with CHD and depression and to identify whether any changes were necessary
				2. Feasibility and piloting	<i>Not reported</i>
				3. Evaluation	<i>Not reported</i>
				4. Implementation	<i>Not reported</i>
Blackwood et al. (2006)	UK	Nurse-led intervention for weaning patients from mechanical ventilation in intensive care unit (ICU)	2000	0. Pre-clinical phase	<ul style="list-style-type: none"> – Literature review to identify key components of intervention – Review of theories of change and behavioural management to identify factors critical for change
				1. Modelling phase	<ul style="list-style-type: none"> – Observation of patients where intervention was to be introduced – Semi-structured interviews with ICU consultants to identify aids and barriers to developing weaning protocols and their introduction to practice – Questionnaire survey for ICU nurses to determine knowledge and attitudes towards weaning
				2. Exploratory phase	<ul style="list-style-type: none"> – Exploratory trial employing quasi-experimental, non-equivalent group design

				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implementation phase	<i>Not reported</i>
				1a. Identifying the evidenced base	<ul style="list-style-type: none"> – Semi-structured interviews with eye-care providers, policy makers and health service commissioners to elicit their experiences and perspectives about the main properties of a potential intervention for a national glaucoma screening trial
				1b. Identifying/developing theory	<i>Not reported</i>
				1c. Modelling the process and outcomes	<ul style="list-style-type: none"> – Economic modelling incorporating data collected from the interviews. – All the potential screening components put forward by the interviewees were summarised in tabular form for consideration in the economic model. New screening strategies were then ordered according to the potential that they would be cost-effective
Burr et al. (2011)	UK	Intervention for glaucoma screening	2008	2. Feasibility and piloting	<i>Not reported</i>
				3. Evaluation	<i>Not reported</i>
				4. Implementation	<i>Not reported</i>
				0. Preclinical phase	<ul style="list-style-type: none"> – Literature search to gain an understanding of prevailing attitudes and identifying and overcoming obstacles to change – Focus groups with HCP to define how to develop a system of shared care
				1. Modelling phase	<ul style="list-style-type: none"> – Proposed conceptual framework for shared care and toolkit were then developed by integrating the data from the focus groups with the literature and ideas from practical experience – Focus groups with HCP and local experts in primary mental health to review toolkit – Revised toolkit
Byng and Jones (2004)	UK	Intervention to improve shared care for patients with long-term mental illness	2000	2. Exploratory phase	<ul style="list-style-type: none"> – Piloting of toolkit in 3 practices – Brief questionnaire with fixed and free text responses to evaluate practitioners' perceptions of the different components of the intervention

					<ul style="list-style-type: none"> – Semi-structured and in-depth interviews with all involved – Reflection of the research team on their experiences of using the model – Further modification based on feedback
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implementation phase	<i>Not reported</i>
Byrne et al. (2006)	Ireland	Healthcare intervention to promote secondary prevention of CHD	2000	0. Preclinical phase	<ul style="list-style-type: none"> – Literature search relating to secondary prevention of CHD – Discussion of research team on key findings regarding successful interventions and identification of findings deemed appropriate to the setting – Looked at theories on health behaviour (theories on lifestyle/behaviour change)
				1. Modelling phase	<ul style="list-style-type: none"> – Focus groups with patients from 4 GP practices to evaluate experiences and attitudes towards key intervention components identified in literature
				2. Exploratory phase	<ul style="list-style-type: none"> – Training of practitioners and evaluation of training – Pilot testing of the preliminary intervention – Semi-structured interviews and focus groups to evaluate patients' experience of the intervention
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>
Carnes et al. (2013)	UK	Self-management intervention for chronic pain patients	2008	1a. Identifying the evidence base	<ul style="list-style-type: none"> – Two systematic reviews to identify effective components and characteristics of pain management courses and predictors, mediators and moderators of outcome in pain management courses – Phenomenological qualitative interview (with chronic pain self-management course participants) and focus group (with experts from those who had recently published in this field and tutors of local Expert Patients Programme providers) study to address what the intervention should focus on

				1b. Identifying or developing theory	– Literature search and spoke to experts on behavioural change theory and models of persisting pain. Considered different theories
				1c. Modelling the process and outcomes	– Mapping of behavioural change theories – Created a consensus group (patients, HCPs, researchers and commissioners) to agree on the outcomes we wanted the intervention to affect and the appropriate measurement tools
				2. Feasibility and piloting	– Uncontrolled pilot study approach to test the feasibility of delivering the intervention and the receipt of the intervention
				3. Evaluation	<i>Not reported</i>
				4. Implementation	<i>Not reported</i>
				1a. Identifying the evidence base	– Literature review to identify potentially inappropriate prescribing criteria and the empirical and theoretical evidence relating to intervention research and altering prescribing practice
				1b. Identifying or developing theory	<i>Merged with previous step</i>
Clyne et al. (2013)	Ireland	Intervention to decrease potentially inappropriate prescribing in older people	2000 and 2008	1c. Modelling the process and outcomes	– Consensus based methodology with experts in the field (GPs, pharmacists, specialist in clinical pharmacology and medicine for the elderly) to decide which criteria to include in the study – Patient case identification to test intervention materials compiled in consensus methodology completing specifically designed evaluation sheets – Focus groups with GPs to evaluate materials – Compiling of information from evaluation sheets and focus groups to further refine intervention
				2. Exploratory phase	– Proposed intervention tested by five GPs – Qualitative interviews with GPs to inform the development and implementation of the intervention for the main RCT
				3. Definitive RCT phase	– Cluster large-scale RCT to assess effectiveness and acceptability of the intervention

					<ul style="list-style-type: none"> – Qualitative interviews at the end of the RCT with patients and GPs to provide insight into the intervention delivery and acceptability of the intervention
Ettema et al. (2015, 2014)	Netherlands	Nursing intervention to prepare frail older patients for cardiac surgery	2008	4. Long-term implantation phase	<i>Not reported</i>
				1a. Identifying the evidenced base	<ul style="list-style-type: none"> – Systematic review to identify studies describing interventions for preparing older patients for a hospital admission for cardiac surgery and the methods that have been used to evaluate these interventions
				1b. Identifying/developing theory	<ul style="list-style-type: none"> – Literature review looking at possible relationships between the preadmission characteristics of older patients and the occurrence of postoperative complications – Analytical (observational) study to model preadmission patient characteristics related to postoperative complications by collecting data from patients in clinic. Comparison of patients having complications and not having complications – Prognostic study using a scorecard to predict postoperative complications in the same sample as the analytical study
				1c. Modelling the process and outcomes	<ul style="list-style-type: none"> – Patient in-depth interviews exploring perceived needs before and during hospital admission – Survey study with cardiac nurses asking their opinion on the prevention, diagnosis and treatment of postoperative complications – Expert round with Dutch national leading experts to test face validity of the content of the intervention – Clinical expert round with cardiac surgeons and cardiac surgery nurses to test the clinical applicability of the intervention
				2. Feasibility and piloting	<i>Not reported</i>
				3. Evaluation	<i>Not reported</i>
				4. Implementation	<i>Not reported</i>
	UK	Palliative	2000	0. Preclinical phase	<ul style="list-style-type: none"> - Qualitative study of lung cancer and COPD patients' experience of breathlessness

Farquhar et al. (2011)		Breathlessness Intervention Service in patients with intractable dyspnoea			- Developed pilot intervention
				1. Modelling phase	- Qualitative interviews with patients and relatives who had used the newly formed pilot palliative breathlessness service and clinicians who had referred to it to evaluate the service - Refined intervention
				2. Exploratory phase	- Mixed method pilot pragmatic single-blind fast track RCT of the re-developed breathlessness service vs. standard care to test the feasibility of the proposed mixed method trial - Collection of quantitative data (response rates, protocol completion rates and field notes) to evaluate feasibility of intervention - Qualitative interviews with patients, carers, referrers and providers of the intervention to evaluate acceptability of the intervention - Further refinement of intervention
				3. Definitive RCT phase	- Plan for mixed method pragmatic single-blind fast track RCT trial of the re-developed breathlessness service vs. standard care integrating: a qualitative topic-guided interview with quantitative outcome measures for patients and carers; a concurrent qualitative interview study with referrers to the service; and sequential qualitative interviews with service providers. This will be conducted to determine the effectiveness of the intervention, reasons for success or failure and reasons for variation.
				4. Long-term implantation phase	<i>Not reported</i>
Faes et al. (2010)	Netherlands	Intervention for complex fall prevention	2000	1a. Identifying the evidenced base	- Descriptive analysis of the characteristics of the cohort - Literature reviews to understand pathways that cause and sustain falls in frail community; of interventions to prevent falls and fear of falling
				1b. Identifying/developing theory	- Semi-structure interviews with frail older patients who experienced falls and primary family caregivers

					<ul style="list-style-type: none"> – Literature reviews of behavioural change theories to reduce fear – Focus group with project team and experts – Non-participatory observation of CBT group and individual therapy to reduce fear
				1c. Modelling the process and outcomes	<ul style="list-style-type: none"> – Second focus group with experts – Semi-structured interviews with experts – Semi-structured interviews with patients and caregivers – Delphi study with specialists – Second non-participatory observation of session for physical therapists, who were trained to deliver a fall prevention intervention for non-frail older persons – Literature review on the available evidence regarding the recruitment and adherence of older persons in aging research – Third non-participatory observation of physical training sessions for demented older persons conducted by physiotherapists
				2. Feasibility and piloting	<ul style="list-style-type: none"> – Test feasibility of the recruitment process, intervention and measurement
				3. Evaluation	<ul style="list-style-type: none"> – Focus group with patients, caregivers, instructors, and researchers – Focus group with researchers and instructors – Questionnaires administered to patients, caregivers, and instructors evaluating the performance of the intervention according to protocol – Third focus group with experts
				4. Implementation	<i>Not yet performed</i>
Gray et al. (2013)	UK	Intervention for weight loss in adult men	2000	0. Preclinical phase	<i>Not reported</i>
				1. Modelling phase	<ul style="list-style-type: none"> - Pilot intervention development by expert multidisciplinary working group (psychologists, health social scientists, nutritionist, men health's nurse, representative of Scottish Premier League) - Scoping review to identify optimal target population: summarising existing evidence on men's motivation to

					lose weight and improve their lifestyles, the potential health benefits of weight loss and increased physical activity and current weight management and physical activity guidance
				2. Exploratory phase	<ul style="list-style-type: none"> - Piloting of intervention - Process evaluation to explore programme delivery from participant and coach viewpoints (feedback form completion and observation of sessions) - Feasibility trial to investigate recruitment, retention and potential weight loss in preparation for subsequent RCT - Semi-structured focus groups with men who completed intervention and telephone or face-to-face interviews with non-completers to explore acceptability, utility of components, suggestions for changes - Semi-structured interviews with those delivering the intervention - Triangulation of data to produce detailed description to inform the redevelopment of the programme
				3. Definitive RCT phase	<ul style="list-style-type: none"> - Two members of the programme development working group used the BCT taxonomy to map the content of the intervention onto specific behaviour change techniques - <i>RCT not reported</i>
				4. Preclinical phase	<i>Not reported</i>
Kirkevold et al. (2012)	Norway	Nursing intervention for psychological health and well-being after stroke	2000 and 2008	1a. Identifying the evidenced base	<ul style="list-style-type: none"> - Review and synthesis of existing qualitative studies for the need of psychological support after a stroke - Review of the literature to identify systematic reviews of post-stroke psychological needs and effectiveness of interventions addressing these needs - Identification of theories to illuminate possible effective mechanisms and actions aimed at promoting psychosocial well-being during the stroke recovery process - Development of intervention aimed at promoting psychosocial wellbeing
				1b. Identifying/developing theory	<i>Merged with previous step</i>

				1c. Modelling the process and outcomes	<ul style="list-style-type: none"> - Evaluation and critique of the proposed intervention by patient and relative representatives, clinical experts and researchers during several expert group meetings - Refinement of intervention
				2. Feasibility and piloting	<i>Not reported</i>
				3. Evaluation	<i>Not reported</i>
				4. Implementation	<i>Not reported</i>
Lewis et al. (2013)	UK	Guided self-help (GSH) intervention for the treatment of mild-to-moderate post-traumatic stress disorder (PTSD)	2000 and 2008	0. Preclinical phase	<i>Not reported</i>
				1. Modelling phase	<ul style="list-style-type: none"> - Identification of existing evidence to create a portfolio of information for key stakeholders - Portfolio presented to stakeholders and their opinions and suggestions gathered through a series of focus groups and semi-structured interviews - Creation of prototype one - Results of qualitative analysis used to create initial prototype GSH programme
				2. Exploratory phase	<ul style="list-style-type: none"> - Pilot of prototype one - Interviews with participants to elicit their experiences of the program - Focus groups with stakeholders to discuss findings and refine programme - Creation of prototype two - Pilot of prototype two - Interviews with participants to elicit their experiences of the program - Focus groups with stakeholders to discuss findings and finalise programme
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>
Lovell et al.	UK	GSH	2000	0. Preclinical phase	<i>Not reported</i>

(2008)		intervention for depression in primary care		1. Modelling phase	<ul style="list-style-type: none"> – Quantitative systematic review and meta-regression to synthesise available evidence of the effectiveness of RCTs with populations suffering from depression – Qualitative meta-synthesis to identify key factors that may moderate effectiveness – Consensus process with experts to interpret the evidence and deal with ambiguities. Questions related to the number, duration and time period of the intervention, how to incorporate and manage issues such as the patient being the agent of change and regaining control, the delivery mode of the guidance, the health technology, and the training and role of health professional delivering the intervention – Matrix of results to combine results of the three – Used matrix for discussion with trial team and derive final intervention
				2. Exploratory phase	<ul style="list-style-type: none"> – Exploratory randomised controlled trial examining: fidelity using analysis of taped guided self-help sessions, acceptability to patients through semi-structured qualitative interviews, preliminary estimation of effect size through comparison of outcomes in patients receiving intervention and those in usual care
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>
Murchie et al. (2007)	UK	Integrated follow-up programme for cutaneous melanoma	2000	0. Preclinical phase	<i>Merged with modelling phase</i>
				1. Modelling phase	<ul style="list-style-type: none"> – Broad ranging iterative literatures review on melanoma, with further focus on intervention development to inform specific aspects of the final design – Steering group (researchers, GPs and hospital specialists working patients with melanoma) meetings to identify possible intervention models – Semi-structured telephone interviews with patients with melanoma and GPs about their thoughts on the intervention

				2. Exploratory phase	<ul style="list-style-type: none"> – Intervention piloted by two GPs (one urban and one rural) to assess feasibility and identify problems and deficiencies – Brief semi-structured interviews with patients who underwent the intervention to understand participants' practical experiences and views on how to optimize the intervention
				3. Definitive RCT phase	<ul style="list-style-type: none"> – Funding for large-scale RCT in place – Parallel qualitative study to provide more information to inform further intervention development if this is necessary <i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>
Palmer et al. (2013)	UK	Nurse-led intervention for the outpatient management of incidentally diagnosed pulmonary embolism in cancer patients	2000	0. Pre-clinical phase	<ul style="list-style-type: none"> – Selected most robust tool for risk assessment and best guideline by looking at a meta-analysis of trials and cohort study – Review of historical registry and audit data from the centre
				1. Modelling phase	<ul style="list-style-type: none"> - Identification of training needs for staff, planning and implementation of training schemes and development of transferable competencies and training material - Mapping patient pathways and flow - Production of key documentation and Standard Operating Procedures for the delivery of the service
				2. Exploratory phase	<i>Not reported</i>
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<ul style="list-style-type: none"> - Pathway implemented - Audit of new pathway
Redfern et al. (2008)	UK	Intervention to improve risk factor management after stroke	2000	0. Preclinical phase	<ul style="list-style-type: none"> – Systematic review to evaluate the effectiveness of interventions to improve risk factor management for CHD and stroke – Statistical analyses of data collected in the stroke register to identify local patterns of secondary prevention management

					<ul style="list-style-type: none"> – Exploratory qualitative interviews to investigate patients' understanding of secondary prevention of stroke and experiences of managing risk factors – Non-participant observations at two hospital stroke outpatient clinics to investigate how prevention advice is given and received – Content analysis of currently available patient information literature addressing secondary prevention (data extracted by two researchers using a structured matrix)
				1. Modelling phase	<ul style="list-style-type: none"> – Compiling of 48 key issues arising from pre-clinical phase and presentation of key issues to all study investigators – Discussion by research team to decide which factors should be addressed in intervention – Presentation of findings to steering group of experts (clinicians, researchers, patients and their family) – Modification of register data collection tools – Testing of new questions on patients and minor modification following feedback – Development of secondary prevention package. Checking by specialist, SMOG test for readability, feedback from patients
				2. Exploratory phase	<ul style="list-style-type: none"> – Pre-trial evaluation of intervention components by testing the complete intervention process – No randomisation – Documentation of all problems encountered – Semi-structured interviews with patients and professionals following the intervention
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>
Robinson et al. (2005)	UK	Intervention to facilitate coping skills in new	2000	0. Preclinical phase	<ul style="list-style-type: none"> - Literature review to identify the needs of carers of people with stroke - Development of intervention based on CBT model and coping theory

		carers of stroke patients		1. Modelling phase	<ul style="list-style-type: none"> – Semi-structured interviews to explore carers' experiences of caring and their views on the proposed theoretical intervention – Refinement of course following interviews
				2. Exploratory phase	<ul style="list-style-type: none"> – Feasibility testing of the course – Interviews conducted with course participants to explore views about content, appropriateness and delivery of the course – Second feasibility testing of course, completion of feedback questionnaires
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>
Smith et al. (2012)	UK	Intervention to reduce time to presentation with lung cancer symptoms	2008	1a. Identifying the evidenced base	<ul style="list-style-type: none"> - Meetings of expert multidisciplinary group (psychologists, sociologist, GPs, respiratory physician, researcher) to: define the problem of patient behaviour leading to late presentation of lung cancer symptoms, identify target group, identify behavioural and social models from health psychology, map theory and evidence on to concrete behaviour change techniques, quantify the potential benefit of the intervention - Synthesis of identified techniques into a first draft of the intervention
				1b. Identifying/developing theory	<i>Merged with prior phase</i>
				1c. Modelling the process and outcomes	<ul style="list-style-type: none"> - Focus groups with GPs, high risk patients and patients with lung cancer to comment on the summary of the intervention - Individual interviews with patients with lung-cancer to comment on the summary of the intervention - Refinement of intervention based on data from focus groups and interviews - Meetings with GPs who had agreed to pilot interventions to identify potential barriers - Coding of manual using 84 behaviour change techniques to identify the precise techniques used in the intervention

				2. Feasibility and piloting	<i>Not reported</i>
				3. Evaluation	<i>Not reported</i>
				4. Implementation	<i>Not reported</i>
Sturt et al. (2006)	UK	Nursing intervention for self-efficacy goal achievement in type 2 diabetes	2000	0. Preclinical phase	<ul style="list-style-type: none"> - Literature analysis and review of findings from parallel studies - Needs analysis of patient diabetes educational needs - Re-validation of Dutch 20-item type 2 Diabetes Self-Efficacy Scale in the UK
				1. Modelling phase	- Small uncontrolled trial of the intervention to evaluate feasibility, identify appropriate outcome measures for future trials and improve components
				2. Exploratory phase	<i>Not reported</i>
				3. Definitive RCT phase	<i>Not reported</i>
				4. Long-term implantation phase	<i>Not reported</i>

Appendix XIX: Amendments to published papers following oral examination

- Paper 1, page 64: Add sentence in Methods section stating: ‘The search was completed in June 2015.’
- Paper 2, page 89: Original sentence stating: ‘Questions in Section 2 are scored on a 0-4 Likert scale, with the possible total score ranging from 0 to 20.’ Correct sentence in Methods section stating: ‘Questions in Section 1 are scored on a 0-4 Likert scale, with the possible total score ranging from 0 to 20.’
- Paper 2, page 92: Original sentence stating: ‘In addition, faecal calprotectin ($r = 0.47$, $P < 0.001$) and platelets ($r = -0.15$, $P < 0.03$) were significantly associated with QoL.’ Correct sentence in Results section stating: ‘In addition, faecal calprotectin ($r = -0.47$, $P < 0.001$) and platelets ($r = -0.15$, $P < 0.03$) were significantly associated with QoL.’
- Paper 2, page 93: In Table 2, the subheadings should be corrected and presented in the order: B (95% CI), *P*-value, ΔR^2 .
- Paper 2, page 95: In Table 3, the subheadings should be corrected and presented in the order: B (95% CI), *P*-value, ΔR^2 .
- Paper 2, page 96: Please find below the missing NS data to be added to Table 4, Columns 2 and 3.

IBF-F1 (Column 2)

Distress = 0.14 (-0.01-0.02), $p = 0.65$

Stress = 0.05 (-0.05-0.12), $p = 0.45$

All-or-nothing = 0.10 (-0.03-0.21), $p = 0.14$

Avoidance = 0.02 (-0.10, 0.13), $p = 0.75$

IBD-F2 (Column 3)

Female gender = -0.006 (-4.71, 4.08), $p = 0.87$

Daytime sleepiness = 0.07 (-0.15, 0.88), $p = 0.16$

- Paper 4, page 156: In Table 4, the legend should be corrected to $p < .05$ from $p < .005$.
- Paper 4, page 147: In Table 2, percentage of patients with previous surgery in Group 1 should be corrected to 6.6%.
- Please find below completed and corrected references. Reference 48 should be deleted and substituted with 41 in text.

10. Williet, N., Sarter, H., Gower-Rousseau, C., Adrianjafy, C., Olympie, A., Buisson, A., Beaugerie, L. and Peyrin-Biroulet, L., 2017. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. *Journal of Crohn's and Colitis*, 11(2), 165-174.
12. Casellas, F., Herrera-de Guise, C., Robles, V., Navarro, E. and Borruel, N., 2017. Patient preferences for inflammatory bowel disease treatment objectives. *Digestive and Liver Disease*, 49(2), 152-156.
35. Hashash, J.G., Ramos-Rivers, C., Youk, A., Chiu, W.K., Duff, K., Regueiro, M., Binion, D.G., Koutroubakis, I., Vachon, A., Benhayon, D. and Dunn, M.A., 2018. Quality of sleep and coexistent psychopathology have significant impact on fatigue burden in patients with inflammatory bowel disease. *Journal of Clinical Gastroenterology*, 52(5), 423-430.
39. McNelly, A.S., Nathan, I., Monti, M., Grimble, G.K., Norton, C., Bredin, F., Czuber-Dochan, W.J., Berliner, S., Gay, M.A., Darvell, M. and Terry, H., 2016. The effect of increasing physical activity and/or omega-3 supplementation on fatigue in inflammatory bowel disease. *Gastrointestinal Nursing*, 14(8), 39-50.
41. Szigethy, E., Mcauliff, K., Strassburger, M., 2016. Brief behavioral therapy and bupropion for sleep and fatigue in adolescents and young adults with inflammatory bowel disease. *Journal of the American Academy of Child and Adolescent Psychiatry*, 55(10), S210
49. Czuber-Dochan, W.J., 2016. *Exploring fatigue in Inflammatory Bowel Disease as experienced by individuals: a descriptive phenomenological study* (Doctoral dissertation, King's College London).
50. Artom, M., Czuber-Dochan, W., Sturt, J. and Norton, C., 2016. Targets for health interventions for inflammatory bowel disease-fatigue. *Journal of Crohn's and Colitis*, 10(7), 860-869.
60. Timmer, A., Preiss, J.C., Motschall, E., R3cker, G., Jantschek, G. and Moser, G., 2011. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Systematic Reviews*, (2), CD006913.
105. Christensen, H., Griffiths, K.M. and Farrer, L., 2009. Adherence in internet interventions for anxiety and depression. *Journal of Medical Internet Research*, 11(2), e13-e13.
116. Ratnakumaran, R. Warren, L., Gracie, D., Sagar, R., Malin, J., et al., 2018. Fatigue in inflammatory bowel disease reflects mood and symptom-reporting behavior rather than biochemical activity or anemia. *Clinical Gastroenterology and Hepatology*, 16 (7), 1165 – 1167

- Please find below table with effect sizes to be added to Paper 4, page 156 in the last column of Table 4.

Outcome	Group	Baseline		3-months follow-up			Change Scores			
		Mean	SD	Mean	SD	N	Mean	SD	MD (CI)	Effect size
IBDF-1	Group 1	11.57	3.60	7.29	3.95	7	-4.29	5.28	-3.10 (-7.10, 0.86)	-0.8
	Group 2	10.64	4.25	9.45	4.55	11	-1.18	2.68		
IBDF-2	Group 1	56.71	32.53	25.71	15.64	7	-31.00	25.72	-26.89 (-51.39, -2.39)*	-1.2
	Group 2	51.44	33.23	47.33	31.12	9	-4.11	20.08		
IBDQ	Group 1	87.60	13.64	95.89	10.58	9	7.33	11.56	3.33 (-6.21, 12.88)	0.3
	Group 2	91.70	9.80	95.70	10.54	10	4.00	8.04		

Appendix XX: Additional chapter with 12-month longitudinal analysis from quantitative study

Introduction

Fatigue is a prevalent concern for patients with IBD, which can have a significant negative impact on patients' quality of life (QoL) (Cohen et al., 2014). Symptoms of fatigue limit patients in their everyday lives, both physically, socially and at work (Beck et al., 2013). Accordingly, the management of fatigue is an important clinical priority in patients with IBD. Despite the high prevalence of fatigue, the causes of fatigue in IBD are not well understood by either patients (Czuber-Dochan et al., 2013b) or health-care professionals (HCPs) (Czuber-Dochan, 2014b); and this far only four non-pharmacological interventions (Vogelaar et al., 2011, 2014, McNelly et al., 2016, Artom et al., 2017) have been targeted for this problem.

While proving excellent prevalence data, the dominance of cross-sectional, population-based studies has limited the exploration of the pathogenesis of fatigue in the IBD clinical population (Artom et al., 2016a). To date, only three studies (Banovic et al., 2010, Graff et al., 2013, Van Langenberg et al., 2014) have looked at longitudinal predictors over time. One study (Graff et al., 2013), found that higher disease activity, emotional distress, lower psychological well-being and poor sleep quality predicted an increase in fatigue over 24 months. Additionally, looking at factors improving fatigue in Crohn's disease over time, Van Langenberg and colleagues (2014) reported that reduction in depression and commencement of a regular exercise programme led to improvements in physical fatigue. Older age, improvement in sleep quality and cessation of immunomodulator therapy were associated with improvements in cognitive fatigue.

A cross-sectional study by our research team (Artom et al., 2016b) found that emotional, cognitive and behavioural factors were associated with fatigue and QoL above and beyond the influence of sociodemographic and clinical factors. Negative fatigue perceptions were significantly associated with severity of fatigue. Negative fatigue perceptions, all-or-nothing and avoidance behaviours were significantly associated with impact of fatigue. However, the direction of association between these factors is still unclear, as are the exact mechanisms of interplay over time. To develop and test treatment models specific to this population, it is therefore important to view fatigue within a biopsychosocial model of care and consider how different clinical, sociodemographic and psychosocial factors interact with each other to predict IBD-fatigue. The aim of current the study was thus to determine the longitudinal course of fatigue in IBD and the contributors to changes in fatigue over 12 months.

Methods

Study design and population

The study followed a 12-months longitudinal design assessing clinical, socio-demographic and psychosocial predictors of fatigue. Participants were recruited between September 2015 and March 2016 from the IBD services (out-patient clinics and biologic infusion units) at three tertiary referral hospitals in London. Patients with a documented diagnosis of IBD, aged 18 and over, with sufficient command of written and spoken English to complete self-report questionnaires were considered eligible for inclusion. Exclusion criteria were known cognitive impairment, currently on intravenous iron therapy, pregnancy or childbirth within the last 6 months. The baseline data from the study are reported in Paper 2. All participants recruited at baseline were sent follow-up questionnaires 12-months after baseline response. Questionnaires were sent via postal mail with a prepaid envelope and patients were asked to return the completed questionnaires to the research team within 7 days from the day of receipt. Non-responders to the follow-up questionnaire were sent a reminder letter via postal mail at 4 weeks after the surveys were disseminated.

Sociodemographic, clinical and psychological data collection

Sociodemographic, clinical and psychological data collection were the same as the baseline study and are presented in Paper 2.

Ethical considerations

The study was approved by the United Kingdom National Research Ethics Service – London Bridge Committee (15/LO/1081). At baseline, eligible patients were provided with a Patient Information Sheet explaining the nature and the aims of the study. Signed informed consent was returned with the study questionnaire by post. Following completion of the consent form at baseline, continued consent for the study was implied by the return of the completed questionnaires at follow-up.

Statistical methods

Statistical analyses were performed using SPSS version 22. Factors associated with the outcomes in univariate analysis at baseline were included in multivariate regression analyses to identify independent predictors of fatigue at 12-months follow-up. Multiple imputation was not used to address missing data and multivariate analysis at 12-months follow-up was conducted on complete cases only. Variables were entered in two regression models (IBD-F1 and IBD-F2) using a two-block variable entry method hierarchical method. Block 1 was adjusted for sociodemographic and clinical predictors of the outcome variable (fatigue at 12-months follow-

up); in block 2, psychosocial variables were added (i.e. adjusted for block 1, sociodemographic and demographic variables).

Results

A total of $n = 414$ patients were approached at baseline for inclusion in the study. Of these 182 patients provided informed consent and returned the completed questionnaires via post (44% response rate). Of these 182, 100 responded at 12-months after one reminder (54.9% response rate). Fifty-one percent were female, 49.5% worked full-time and their median age was 44.5 years (range 20-83 years). The majority (64.2%) of participants had CD. Of the 62.4% of patients taking medication, 42% were on biologic medication (anti-TNFs or vedolizumab), and one participant had a stoma.

Factors associated with severity of fatigue (IBD-F1)

Significant factors in univariate analyses in respect to severity of fatigue at baseline ($p < 0.10$) were examined in a two-block regression model for the IBD-F1 at 12-months follow-up (Table 1). Female gender, divorced/widowed marital status and baseline disease activity significantly predicted fatigue at 12-months follow-up, explaining 17% of the variance in severity of fatigue scores. The emotional, cognitive and behavioural variables that were added in the second block explained 24% of the variance in fatigue severity scores at 12-months follow-up. However, they did not significantly improve the predictive validity of the model, $F_{\text{inc}}(13, 52) = 1.46, p = 0.16$. More negative fatigue perceptions significantly predicted greater IBD-F1 scores at 12-months follow-up. After adjusting for psychosocial variables, divorced/widowed marital status ($b = 0.29, p = 0.02$) and baseline disease activity still significantly predicted greater IBD-F1 scores at 12-months follow-up. Female gender ($b = 0.21, p = -0.10$) was no longer significant.

Factors associated with impact of fatigue (IBD-F2) in individuals' lives

Significant factors in univariate analyses in respect to impact of fatigue at baseline ($p < 0.10$) were examined in a two-block regression model for the IBD-F2 (Table 2). Education up to 18 negatively predicted impact of fatigue, where patients with higher levels of education had significantly lower levels of fatigue impact at 12-months follow up ($p = 0.03$). Baseline sociodemographic and clinical variables explained 10% of the variance in impact of fatigue scores at 12-months follow-up. The emotional, cognitive and behavioural variables that were added in the second block explained 12% of the variance in impact of fatigue scores at 12-months follow-up, not significantly improving the predictive validity of the model $F_{\text{inc}}(13, 50) = 1.60, p = 0.12$. None of the emotional, cognitive and behavioural variables added in the second block significantly predicted impact of fatigue at 12-months follow-up ($p > 0.05$).

Table 1: Hierarchical regression of sociodemographic, clinical and psychosocial baseline and longitudinal predictors of fatigue severity.

	Baseline IBD-F1			12-months IBD-F1		
	<i>B</i> (95% CI)	<i>P</i> - <i>value</i>	ΔR^2	<i>B</i> (95% CI)	<i>P</i> - <i>value</i>	ΔR^2
STEP 1			.21			.17
Sociodemographic						
Education to 16	0.62 (-1.90, 3.13)	0.63		-0.03 (-3.80, 3.05)	0.82	
Education to 18	1.67 (-0.45, 3.80)	0.12		-0.20 (-5.40, 0.44)	0.09	
Retired	-1.83 (-4.48, 0.82)	0.17		-0.01 (-3.32, 2.98)	0.91	
Not working	1.22 (-0.72, 3.15)	0.22		-0.1 (-5.27, 0.83)	0.15	
Female gender	1.61 (0.15, 3.07)	0.03		0.26 (0.25, 4.60)	0.03	
Single/S parent	-0.44 (-2.00, 1.12)	0.58		0.01 (-9.65, 10.67)	0.92	
Divorced/Widowed	0.75 (-3.57, 5.07)	0.73		0.25 (0.62, 11.39)	0.03	
Clinical						
Disease activity	0.27 (0.07, 0.46)	0.01		0.28 (0.04, 0.73)	0.03	
Exercise <30 minutes	0.66 (-0.84, 2.16)	0.38		-0.12 (-3.26, 0.94)	0.27	
Smoking current	0.36 (-2.86, 3.58)	0.82		0.02 (-4.12, 4.89)	0.86	
Smoking ex	0.21 (-1.50, 1.91)	0.81		0.03 (-1.97, 2.47)	0.82	
Thiopurines	-1.17 (-2.60, 0.27)	0.11		0.14 (-0.96, 3.63)	0.25	
STEP 2			.54			.24
Emotional						
Anxiety	0.04 (-0.17, 2.56)	0.68		0.08 (-0.33, 0.52)	0.66	
Depression	-0.09 (-0.32, 0.14)	0.44		-0.04 (-0.60, 0.46)	0.79	
Distress	0.01 (-0.01, 0.01)	0.67		-0.10 (-0.03, 0.02)	0.57	
Stress	-0.06 (-0.7, 0.19)	0.39		-0.10 (-0.03, 0.02)	0.54	
Cognitive						
Negative fatigue perceptions	0.28 (0.20, 0.36)	<0.001		0.43 (0.08, 0.39)	0.01	
Catastrophising	0.01 (-0.19, 0.21)	0.92		0.14 (-0.18, 0.54)	0.32	
Damage beliefs	0.08 (-0.11, 0.26)	0.40		0.09 (-0.27, 0.49)	0.57	
Embarrassment	-0.08 (-0.22, 0.05)	0.20		-0.04 (-0.32, 0.25)	0.80	
Fear avoidance	-0.07 (-0.21, 0.08)	0.37		-0.03 (-0.31, 0.24)	0.82	
Symptom focus	0.08 (-0.08, 0.25)	0.34		0.20 (-0.17, 0.57)	0.28	
Behavioural						
All-or-nothing	0.07 (-0.07, 0.22)	0.31		-0.08 (-0.42, 0.23)	0.57	
Avoidance	0.11 (-0.05, 0.26)	0.17		0.11 (-0.41, 0.21)	0.52	
Daytime sleepiness	0.14 (0.01, 0.28)	0.04		0.05 (-0.24, 0.35)	0.73	

Figures in bold are statistically significant at $p < 0.01$; IBD-F1 Fatigue severity

Key: ΔR^2 - Adjusted R Square; **Anti-TNF**- anti-tumour necrosis factor; **ASA**- aminosalicylates; **CI** – confidence interval; **IBD-F** – Inflammatory Bowel Disease-Fatigue Scale

Table 2: Hierarchical regression of sociodemographic, clinical and psychosocial baseline and longitudinal predictors of impact of fatigue on daily activities.

	Baseline IBD-F2			12-months IBD-F2		
	<i>B</i> (95% CI)	<i>P</i> - <i>value</i>	ΔR^2	<i>B</i> (95% CI)	<i>P</i> - <i>value</i>	ΔR^2
STEP 1			.32			.01
Sociodemographic						
Education to 16	-3.95 (-17.64, 9.74)	0.57		0.12 (-10.15, 25.82)	0.39	
Education to 18	2.36 (-8.73, 13.44)	0.67		-0.29 (-31.47, -1.54)	0.03	
Retired	-4.33 (-17.57, 8.90)	0.52		-0.03 (-18.08, 14.11)	0.81	
Not working	12.95 (2.88, 23.01)	0.01		-0.17 (-26.24, 4.68)	0.17	
Female gender	5.32 (-2.25, 12.88)	0.17		0.01 (-10.87, 11.70)	0.94	
Clinical						
5-ASA	-2.29 (-10.55, 5.97)	0.58		0.10 (-7.81, 17.25)	0.45	
Anti-TNF	11.30 (3.53, 19.07)	0.01		0.12 (-5.69, 15.96)	0.35	
Disease activity	2.17 (1.21, 3.13)	< 0.001		0.14 (-0.81, 2.80)	0.27	
Exercise <30 minutes	1.98 (-6.01, 9.96)	0.62		-0.07 (-14.00, 7.58)	0.55	
Steroids	12.72 (-1.32, 26.76)	0.75		-0.13 (-50.27, 15.94)	0.30	
STEP 2			.73			.12
Emotional						
Anxiety	-0.45 (-1.35, 0.45)	0.32		0.02 (-2.36, 2.11)	0.91	
Depression	0.75 (-0.24, 1.74)	0.13		0.13 (-1.5, 3.57)	0.43	
Distress	0.06 (0.01, 0.11)	0.02		-0.30 (-0.23, 0.04)	0.17	
Stress	0.65 (0.09, 1.21)	0.03		0.11 (-1.06, 1.94)	0.56	
Cognitive						
Negative fatigue perceptions	0.55 (0.12, 0.78)	0.01		0.18 (-0.33, 1.26)	0.25	
Catastrophising	0.49 (-0.36, 1.34)	0.26		0.28 (-0.33, 3.67)	0.10	
Damage beliefs	-0.17 (-0.93, 0.59)	0.65		-0.52 (-2.15, 1.57)	0.75	
Embarrassment	0.06 (-0.49, 0.62)	0.82		0.18 (-0.73, 2.11)	0.33	
Fear avoidance	0.13 (-0.49, 0.75)	0.68		0.18 (-0.68, 2.23)	0.29	
Symptom focus	-0.16 (-0.88, 0.55)	0.65		0.05 (-1.72, 2.18)	0.82	
Behavioural						
All-or-nothing	0.86 (0.25, 1.48)	0.01		0.02 (-1.70, 1.91)	0.90	
Avoidance	1.31 (0.65, 1.98)	< 0.001		0.04 (-1.69, 1.91)	0.87	
Daytime sleepiness	0.27 (-0.30, 0.84)	0.35		0.07 (-1.13, 1.85)	0.63	

Figures in bold are statistically significant at $p < 0.01$; IBD-F2 Fatigue impact on daily activities

Key: ΔR^2 - Adjusted R Square; **Anti-TNF**- anti-tumour necrosis factor; **ASA**- aminosalicylates; **CI** – confidence interval; **IBD-F** – Inflammatory Bowel Disease-Fatigue Scale

Discussion

The current study aimed to investigate factors predicting severity and impact of fatigue in patients with IBD. Specifically, it investigated whether modifiable emotional, cognitive and behaviour

factors shown to be associated with fatigue cross-sectionally (Artom et al., 2016b), also predicted fatigue longitudinally at 12-months follow-up. The results of the study showed that baseline cognitive factors predicted severity of fatigue at 12-months follow-up. Negative fatigue perceptions, i.e. feeling of not having control over their fatigue or perceiving fatigue as having more negative consequences, at baseline significantly predicted severity of fatigue over time. However, no emotional, cognitive or behavioural factors significantly associated with impact of fatigue at baseline predicted impact of fatigue at 12-months follow-up.

The main strength of this study was the longitudinal design assessing predictors of fatigue over time. Prior cross-sectional studies cannot readily address the direction of relationships between fatigue and other disease and psychological factors. However, the findings of the study should be considered in light of some limitations. The significant correlations between the psychological measures included in the regression models may indicate a cross-validation between overlapping measures, further analysis is therefore needed in order to reach more definitive conclusions on the fatigue pathways. The moderate sample size at baseline and the additional loss to follow-up at 12-months precluded the exploration of differences according to diagnosis type, potentially limiting the generalisability of the study. The missing data and the lack of use of multiple imputation methods to handle it at follow-up may have affected the robustness of the regression models.

The fact that some psychological factors predicted severity of fatigue in IBD over time support the utility of approaching fatigue multidimensionally, utilising a biopsychosocial approach. When fatigue is evidently related to a flare of IBD or other clinical factors, medical or surgical therapy should be the first line of intervention. However, when there is no apparent explanation for fatigue, exploring psychosocial factors contributing to the onset and maintenance of fatigue may be of value. The study identified novel and potentially modifiable factors associated with fatigue in IBD providing future opportunities for further investigation and clinical application. Ultimately, further prospective interventional studies testing psychological interventions targeted at IBD-fatigue specifically are needed to confirm these findings.